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COMPARISON OF RIGID AND FLEXIBLE ESOPHAGOSCOPY IN THE DIAGNOSIS OF ESOPHAGEAL DISEASE: DIAGNOSTIC ACCURACY, COMPLICATIONS, AND COST

INTRALESIONAL VINBLASTINE FOR TREATING AIDS-ASSOCIATED KAPOSI'S SARCOMA OF THE OROPHARYNX AND LARYNX

ATLANTO-AXIAL SUBLUXATION AND CERVICAL OSTEOMYELITIS: TWO UNUSUAL COMPLICATIONS OF ADENOIDECTOMY

CARCINOMA OF THE ANTERIOR COMMISSURE OF THE LARYNX: I. EMBRYOLOGICAL AND ANATOMIC CONSIDERATIONS

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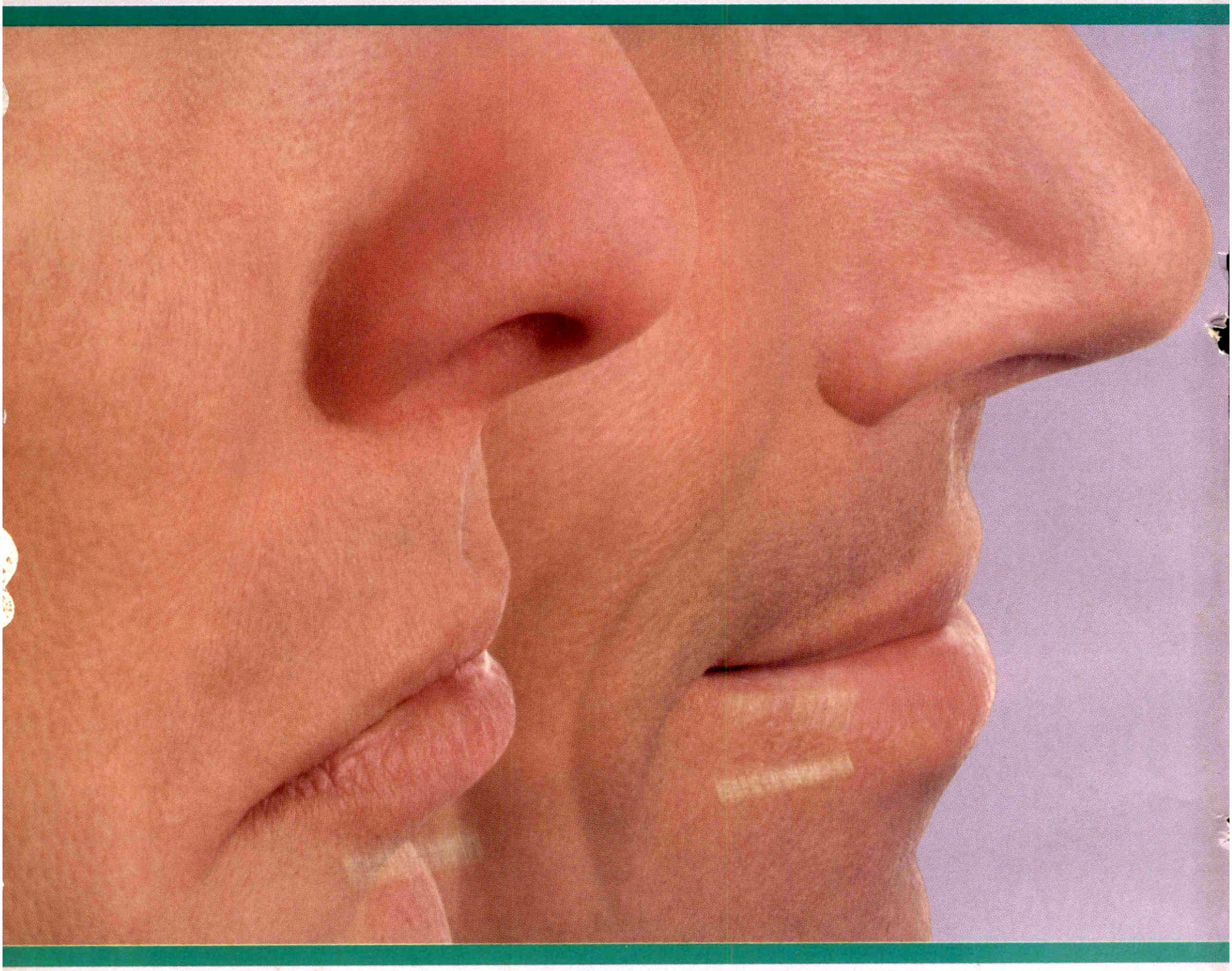

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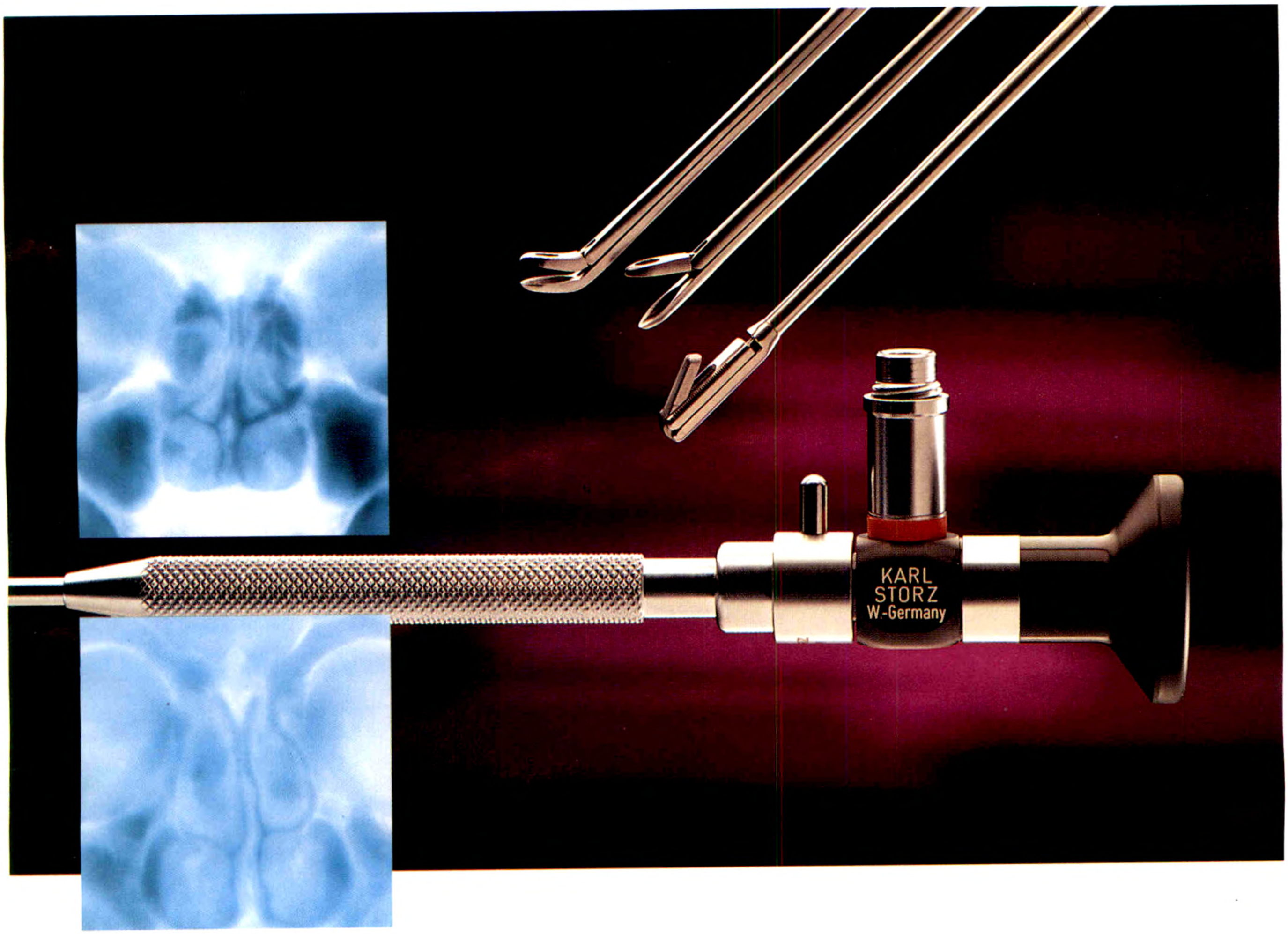

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SUBGLOTTIC AIR PRESSURE: A KEY COMPONENT OF SWALLOWING EFFICIENCY

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The relationship between tracheostomy and swallowing dysfunction has been long recognized. Often this dysfunction is manifested by aspiration, for which a number of etiologic factors may be responsible. Disruption of glottic closure has been previously demonstrated in association with the presence of an indwelling tracheostomy tube. The plugging or removal of the tracheostomy tube, or the use of an expiratory air valve, has been demonstrated to decrease aspiration and improve swallowing function. Measurement of subglottic pressure through an indwelling tracheostomy tube during swallowing demonstrated pressure peaks occurring concomitant with swallowing and laryngeal elevation. This presentation will review the evidence supporting the role of subglottic pressure rise in swallowing efficiency. Current investigational activity will be reviewed, and new areas for study will be suggested.

KEY WORDS — aspiration, dysphagia, subglottic air pressure, swallowing, tracheostomy.

INTRODUCTION

Various factors are known to have an adverse effect on the ability to swallow. Despite the primitive requirement for deglutition, a high level of complex and reflex-mediated neuromuscular functions is required to efficiently control and move a bolus of food or liquid rapidly past the temporarily closed airway. These functions are very susceptible to abnormalities occurring in various mechanical, muscular, and neural control systems. The wide range of abnormalities is beyond the scope of this communication, but spans nearly the entire range of neuromuscular disease, as well as diseases of the mucosal lining and submucosal structures of the oral cavity, pharynx, and esophagus. The exact pathophysiology is often easily ascertained, such as swallowing difficulties due to pain, tumor, muscle weakness, specific cranial neuropathy, or central nervous system dysfunction. In other instances, the etiologic factors are not as easily discerned. At times, a relatively innocuous-appearing and seemingly unassociated injury or intervention can result in significant swallowing dysfunction, which often appears out of proportion to the degree of intervention. An examination of the pathophysiology of the adverse effect on swallowing of these interventions may lead to a deeper understanding of the physiology of normal swallowing. Perhaps even more significantly, this knowledge may suggest strategies useful for the rehabilitation of patients with acquired swallowing disorders.

TRACHEOSTOMY AND ASPIRATION

Perhaps the most interesting, and best studied, of these "interventions" is the performance of tracheostomy.[1,2] It has long been recognized that the performance of a tracheostomy predisposes patients to aspiration. Studies performed several decades ago revealed that dye placed in the oral cavity of patients with tracheostomies was commonly found later in the tracheal secretions of these patients.[3] Even more striking is the effect of tracheostomy on aspiration in patients with concurrent oral pharyngeal dysfunction such as that due to head and neck surgery or neuromuscular disease. Aspiration is often apparent immediately following the performance of a tracheostomy, as evidenced by the presence of clear saliva in and around the tracheostomy tube. In many instances the clinical situation suggests that this aspiration did not exist prior to the performance of the tracheostomy. The cause of this aspiration is probably multifactorial (Table 1).

Removal of the tracheostomy in aspirating patients frequently results in significant improvement in their

TABLE 1. TRACHEOSTOMY AND ASPIRATION PATHOPHYSIOLOGY

- Reduced laryngeal elevation
    - Pain
    - Mechanical tethering
- Reduced cough effectiveness
    - Reduced tracheal sensitivity
    - Inability to clear subglottic trachea
- Relative esophageal obstruction
    - Tracheostomy tube cuff
- Disruption of phasic glottic function
- Blunting of glottic closure reflex (loss of proprioception)

From the Department of Otolaryngology–Head and Neck Surgery, University of Pittsburgh School of Medicine (both authors), and the Department of Communication Science and Disorders, University of Pittsburgh (Gross), Pittsburgh, Pennsylvania. Supported in part by the John R. McCune Charitable Trust Foundation and the Mary Hillman Jennings Foundation.

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swallowing and reduction of aspiration. In many head and neck centers, swallowing rehabilitation in postoperative patients is not instituted until after decannulation. Decannulation is an early goal to reduce the aspiration that is likely to be a major source of morbidity in these patients.

Perhaps the most notable example of the benefit of decannulation can be seen in patients who have undergone supraglottic laryngectomies. The normal supraglottic protective mechanisms are inoperative, and the discomfort of the surgical procedure results in decreased laryngeal elevation. Aspiration is universally severe in these patients following surgery, and persists despite decannulation. Several causes have been suggested for this aspiration:

1. Loss of supraglottic mechanical protection.
2. Loss of supraglottic sensation.
3. Loss of laryngeal elevation due to surgical interruption of laryngeal elevators.
4. Proximity of glottis to tongue base.

Various forms of therapy have been demonstrated to be effective in these patients. Primarily, these include decannulation and learning of compensatory swallowing techniques. Often these same techniques are effective in other aspirating patients with tracheostomies. We have recently demonstrated that the use of a one-way speaking valve is also beneficial in decreasing aspiration in some patients with tracheostomies.[4] The loss of subglottic air pressure and glottic airflow seem to be the active factors in promoting aspiration in these patients. Restoration of a closed subglottic system by decannulation or a one-way speaking valve is key to rehabilitation of many of these patients.

EFFICIENCY ESTIMATES OF SWALLOWING

Various measurements can be used to define the efficiency of swallowing. Rademaker et al[5] have proposed using a combination of various measurements to produce an efficiency score. Perhaps the most clinically apparent of the measures is the presence or absence of aspiration. Although aspiration is due to specific laryngeal incompetence in many instances, it is generally appreciated that in the majority of cases there is an associated oral and/or pharyngeal dysfunction. Videofluoroscopic examinations of aspirating patients indicate that the mechanism of aspiration varies from patient to patient. These mechanisms can be divided roughly into three categories according to time of aspiration: before the swallow is initiated, during the swallow, or after the swallow has been completed.[6]

Aspiration is demonstrated in the first group of patients by videofluoroscopic examination in which loss of the bolus from the oral cavity into the hypopharynx and airway occurs prior to laryngeal elevation and glottic closure. This type of aspiration is common in individuals with generalized disability and weakness and is associated with poor oral motor control. Premature loss of the bolus into the pharynx may be of minimal clinical significance if it results in penetration of the laryngeal vestibule only, and not true aspiration.

The second group of patients will be seen to aspirate during the passage of the bolus through the pharynx in an otherwise normal fashion. This type of aspiration is usually secondary to glottic insufficiency and may be either structural or neurologic in nature. Often, restoration of intact glottic sphincteric function via vocal fold medialization is effective in reducing glottic penetration in these cases. There is associated lack of laryngeal elevation in some of the patients, resulting in lack of the normal protection offered by the tongue base.

A third group of aspirating patients are those with neurologic or gastrointestinal dysfunction resulting in delayed transport of the bolus through the pharynx into the upper esophagus. This can be due to decreased constrictor muscle function at the time of the swallow, delayed opening of the cricopharyngeal sphincter, or a combination of these and other factors. The net result is aspiration of persistent pharyngeal contents at the time of the next glottic opening. If failure of cricopharyngeal relaxation is a factor in these patients, aspiration can occasionally be decreased or eliminated by the performance of a cricopharyngeal myotomy, permitting more rapid emptying of the pharynx. This type of aspiration is commonly associated with a Zenker's diverticulum and is eliminated by cricopharyngeal myotomy and removal of the diverticulum.

PHARYNGEAL CLEARANCE

Another measure of swallowing efficiency is the ability of the pharynx to strip the bolus into the cervical esophagus. Failure to completely empty the pharynx with swallowing is common and can be associated with a wide range of oral and pharyngeal disabilities. Surgery of the head and neck involving the oral cavity, oral pharynx, or hypopharynx can contribute to lack of clearance through the loss of sphincteric function, loss of velopharyngeal closure, loss of tongue mobility, lack of mucosal sensation, or a combination of some or all of these deficiencies. A recent multi-institutional investigation demonstrated a relationship between the extent of surgical extirpation, as well as the technique of reconstruction, and swallowing function.[7]

Patients who suffer neurologic insults or neuromuscular disease will frequently demonstrate decreased pharyngeal clearance. Patients with overt or subtle disability may require several swallows to clear the bolus from the pharynx, even without frank aspiration. Instructing the patient to swallow several times prior to inspiring is often helpful in reducing aspiration associated with decreased pharyngeal clearance. A liquid wash is often helpful in these patients as well. As previously noted, cricopharyngeal myotomy in selected patients may be beneficial in improving the emptying of the pharynx, particularly for isolated constrictor muscle dysfunction.

TIMING OF SWALLOW

A third measure of swallowing efficiency is timing of the events occurring during the swallow.[8] Simultaneous measurement of pressure changes occurring during swallowing via manofluorography can provide accurate timing of swallowing events.[9] It is known that in normal subjects a swallow requires approximately 750 milliseconds from bolus presentation to pharyngeal clearance of the bolus. Prolongation of bolus transit time may result in clinical aspiration, or be associated with reduction of clearance of pharyngeal contents. As an independent measure, bolus transit time represents a measurable quantity useful in comparing swallowing efficiency. Transit time may be defined as the time required for the head of a bolus to pass the mandibular angle so that the tail of the bolus is within the cricopharyngeal sphincter.[10]

The various means of defining swallowing efficiency are, by nature, "soft" measurements. Many of the measures are represented by estimated, rather than easily reproducible, measurements. Factors such as interexamination variability, fluoroscopic magnification, and movement all play a part in reducing the accuracy of measurement. Nevertheless, with experience, certain trends can be noted by the experienced examiner when reviewing videofluoroscopic examinations of patients.

SUBGLOTTIC AIR PRESSURE AND ASPIRATION

Ikari and Sasaki[11] demonstrated that phasic glottic function is lost in the presence of a tracheostomy. Moreover, they have shown that changes in subglottic pressure have a measurable effect on cricothyroid muscle activity. They have postulated that subglottic pressure is key for an intact glottic closure reflex.

We postulated that improvement in swallowing efficiency could be generated by the use of a Passy-Muir Valve (PMV) as well as decannulation. We studied 11 patients with tracheostomies who were known to aspirate with modified barium swallow studies. These swallow studies were repeated with and without a PMV in place and in each of 11 cases there was noted to be either significant decrease or elimination of aspiration with the PMV on the tube. Several of these patients who had been G-tube–dependent were able to resume a normal diet with the use of the PMV as the primary intervention. We postulate that the restoration of normal subglottic pressures by the PMV was key in this clinical improvement.[4] Similar findings have been identified by Stackler et al.[12] Eleven patients were studied by scintigraphy with and without a PMV in place. The scintigraphic studies objectively confirmed the significant reduction in the percentage of boluses aspirated with the PMV in place.[12]

Measurements of subglottic air pressure and airflow through the tracheostomy in selected patients with a tracheostomy were made during swallowing. Pressure and flow measurements were taken with a pneumotachometer with pressure and flow transducers (Setra Systems, Acton, Mass) connected to a side port on an adapter attached to a standard tracheostomy tube. Perci software (Microtonics, Carrboro, NC) was used for analysis. As expected, there was only a minimal rise in pressure during a swallow with the tracheostomy tube open. There was, however, significant expiratory airflow that occurred during the swallow (Fig 1A). With a PMV in place, however, airflow ceased and there was a pressure peak that occurred at the time of the swallow, averaging 10 cm H2O (Fig 1B). The configuration of this peak varied with the type of bolus being swallowed. A modified barium swallow study was performed and the patients were found to aspirate with an open tracheostomy tube when the pressure peak did not occur, and did not aspirate with the PMV in place, with pressure peaks measured between 8 and 10 cm H2O.

VELOCITY OF SWALLOW

An incidental finding noted on early studies utilizing videofluoroscopy in tracheostomized patients suggested that the bolus moved more rapidly through the pharynx into the esophagus with the PMV attached to the tracheostomy tube. On the basis of this observation, we elected to time the bolus in 3 selected patients, comparing velocity with and without the PMV mounted on the tube. Timing was measured by a modification of the Kahrilas technique.[10] The pharyngeal phase in our examination was defined as beginning when the head of the bolus reached the mandibular angle and ending when the tail of the

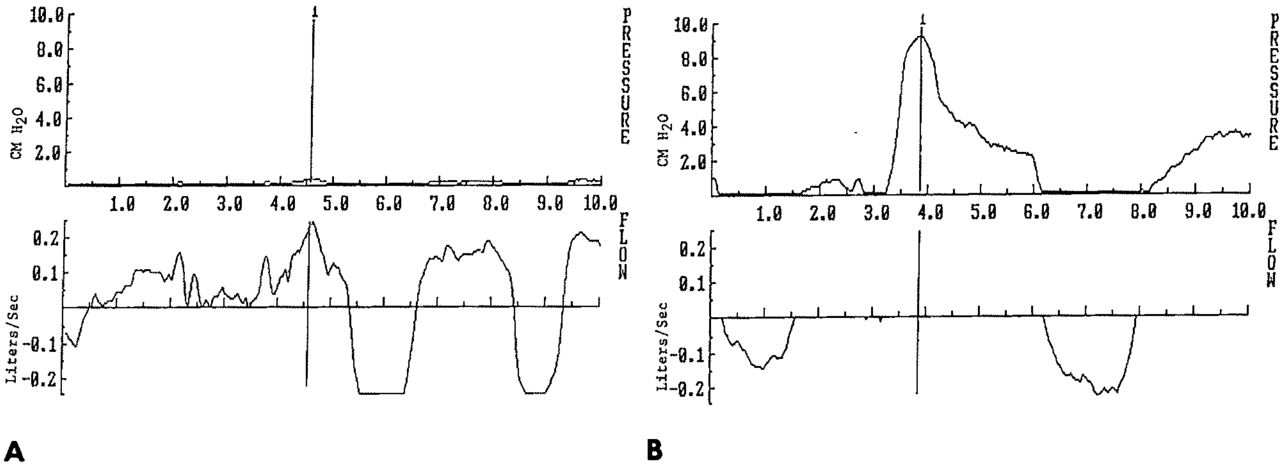

Fig 1. Pressure (top) and flow (bottom) through tracheostomy tube of patient during water swallow. A) Note expiratory airflow occurring during swallow (at 4.5 seconds). B) With Passy-Muir Valve mounted on tracheostomy tube. Note absence of expiratory airflow and positive pressure occurring during swallow (at 3.9 seconds).

bolus was three frames past its visualization within the sphincter. The three-frame delay ensured that the tail of the bolus had completely passed through the cricopharyngeal sphincter.

Examination of timing in these 3 patients supported the clinical observation that velocity was increased (Table 2). Two of 3 patients demonstrated a reduction in transit time of approximately 0.2 second. These studies are preliminary and will require additional investigation for confirmation.

DISCUSSION

The predisposition to aspirate with an open tracheostomy tube is now well recognized. Decannulation is known to benefit many of these patients by reducing or eliminating aspiration. Moreover, we have now shown that the use of a one-way speaking valve will also result in improvement.[4] We now attempt to rehabilitate swallowing in patients with a tracheostomy who aspirate by placing a PMV (Fig 2[13]). Although this maneuver does not resolve difficulties in all tracheostomized patients who aspirate, in many it has provided long-term relief of aspiration. In some patients, reconstitution of glottic competence with vocal cord medialization has been necessary. This effect is not surprising when viewed in light of the work by Sasaki and Isaacson[14] demonstrating the interdependence of subglottic air pressure and the glottic closure reflex.

TABLE 2. PHARYNGEAL TRANSIT TIME

		Duration of Swallow (s)		
Patient No.	*Consistency*	*Without PMV*	*With PMV*	*Difference*
1	Thin liquid	0.858	0.627	0.231
2	Puree	0.742	0.610	0.132
3	Thick liquid	0.825	0.627	0.198

PMV — Passy-Muir Valve.

Subglottic air pressure is known to vary during the normal respiratory cycle. Vocal cord adduction occurs during expiration, resulting in a "braking" effect that increases airway pressure and extends expiratory time.[15] Stretch receptors located in the membranous trachea have been demonstrated to have an inhibitory effect on the respiratory muscles,[16] possibly delaying inspiration until the end of expiration during normal respiration. We postulate that these mechanoreceptors may also function during swallowing to interrupt inspiration. The presence of a tracheostomy prevents the subglottic pressure rise associated with normal swallowing, and may thereby reduce or eliminate the inhibitory effect of the stretch receptors. These findings also suggest that medialization thyroplasty may benefit swallowing in patients with vocal cord pa-

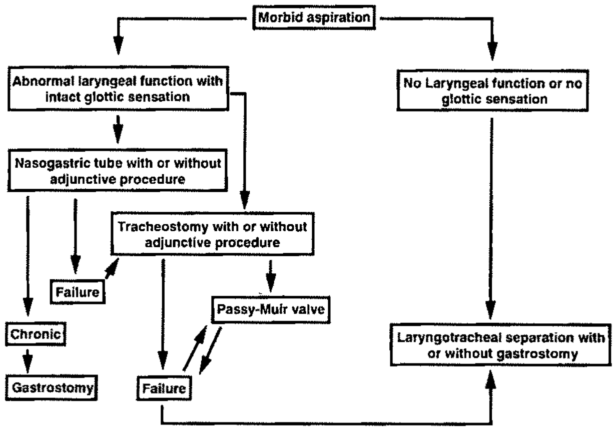
Morbid aspiration
Abnormal laryngeal function with intact glottic sensation
No Laryngeal function or no glottic sensation
Nasogastric tube with or without adjunctive procedure
Tracheostomy with or without adjunctive procedure
Failure
Passy-Muir valve
Chronic
Laryngotracheal separation with or without gastrostomy
Gastrostomy
Failure

Fig 2. Algorithm utilized in our institution for management of patients with aspiration. Note that Passy-Muir Valve will be tried in patients with tracheostomy who aspirate but have intact glottic sensation, in effort to reduce aspiration before proceeding with laryngotracheal separation. (Modified and used with permission from Snyderman et al.[13])

TABLE 3. MANEUVERS TO INCREASE SUBGLOTTIC PRESSURE DURING SWALLOWING

Decannulation
One-way speaking valve (Passy-Muir Valve or similar valve)
Enhancement of glottic competence
Medialization thyroplasty
Vocal cord injection
"Supraglottic" swallow
Generalized muscle strengthening
"In line" Passy-Muir Valve on chronically ventilated patients

ralysis, not only by preventing penetration of liquids, but also by preventing escape of air through the closed glottis. Subglottic pressure peaks during swallowing have been previously measured by Shin et al.[17] They measured pressures both in a cat model and in normal human subjects via a transnasal catheter. In both the feline model and the human subjects a double peak was noted, similar to the modified swallow in our subjects.

The relationship between the respiratory cycle and the timing of deglutition has been studied by Shaker et al.[18] They have demonstrated that deglutition tends to occur during expiration. This finding further supports the hypothesis that positive subglottic pressure during swallowing is required for an efficient swallow. Our observation that velocity of swallowing seems to be enhanced by the restoration of positive subglottic pressure during swallowing may be a significant new finding. Whether this is an independent and unrelated observation, or indeed, whether this is one of the significant factors in the elimination or reduction of aspiration remains to be determined and is currently under further investigation at our institution. It could be postulated that the decrease in aspiration is due to the decreased time that the larynx is "at risk" secondary to the change in velocity of bolus transit through the pharynx. The exact mechanism whereby velocity is increased by the presence of subglottic pressure is open to significant speculation. We postulate that mechanoreceptors located in the subglottis may be an important factor. The interrelationship of the glottic closure reflex, as well as cricothyroid muscle activity, and changing subglottic pressure has been demonstrated by Ikari and Sasaki[11] and Sasaki and Buckwalter.[19] It may be that the effect of these mechanoreceptors extends beyond the intrinsic laryngeal and respiratory muscles to include the pharyngeal muscles as well.

Another possibility is a purely mechanical causation, whereby the presence of subglottic pressure provides "stiffness" to the glottic structures, decreasing the distensible volume of the swallow and avoiding dissipation of intrabolus pressures occurring during the swallow. Over 100 years ago, Brenton, working with cadaver larynxes (cited by Sasaki and Buckwalter[19]) demonstrated that the valve effect of the supraglottic structures alone can generate a resistance of 30 cm H_2O to expiratory airflow. The anatomic and physiologic relationships between the upper respiratory tract and the alimentary tract result in the postulation of a number of etiologic relationships. It is likely that there is not a single mechanism whereby subglottic air pressure enhances swallowing velocity, but rather, that there is a combination of factors. Nevertheless, this observation provides not only evidence for physiologic interrelationship but also opportunities for the development of strategies to improve swallowing function in patients with swallowing disability.

CONCLUSIONS

The maintenance of a closed subglottic system that permits pressure elevation is key to swallowing efficiency. This fact is borne out by a number of clinical and investigational observations. Restoration of positive subglottic pressure appears to be key in enhancing swallowing function following tracheostomy (Table 3). This restoration can be accomplished by decannulation, plugging, or placement of an expiratory speaking valve. Restoration of glottic competence by surgical maneuvers may be needed as well. Alternative methods such as artificial air injection or indwelling subglottic inflatable balloons may be feasible and should be investigated.

The clinical observations noted raise further physiologic questions. The mechanism of the suspected mechanoreceptor function and the physics of mechanical stenting of the glottis require additional study. Further objective measurements of bolus aspiration and timing variations should be performed to confirm these preliminary findings. An understanding of the relationship between respiration and deglutition has the potential to suggest additional strategies to assist in the rehabilitation of patients with swallowing dysfunction.

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EPITHELIAL HYPERPLASTIC LESIONS OF THE LARYNX

The International Conference on Epithelial Hyperplastic Lesions of the Larynx will be held October 28-30, 1996, in Ljubljana, Slovenia. For more information, contact Bostjan Luzar, MD, or Aleksandar Vodovnik, MD, Institute of Pathology, Korytkova 2, 61105 Ljubljana, Slovenia; telephone 386 61 1403042 (Int. 268); fax 386 61 301 816; E-mail Vodovnik@IBMI.MF.UNI-LJ.SI.

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TOTAL TRACHEOBRONCHIAL THROMBOSIS DUE TO EXTRACORPOREAL MEMBRANE OXYGENATION

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Extracorporeal membrane oxygenation (ECMO) is widely used for neonatal respiratory failure that is potentially reversible but unresponsive to conventional management. Because of the anticoagulation necessary for maintaining the extracorporeal circuit, hemorrhagic complications occur in up to one third of patients. We present an unusual and previously unreported complication of ECMO, total tracheobronchial thrombosis. The thrombus filled the entire lower respiratory tract and resulted in airway obstruction and inability to ventilate. The airway was successfully managed with repeated bronchoscopic pulmonary toilet. Our experience and review of the literature provide a summary of ECMO-related complications likely to present to the otolaryngologist, and management strategies are discussed.

KEY WORDS — airway obstruction, extracorporeal membrane oxygenation, thrombosis.

CASE REPORT

A 2-year-old boy underwent surgical repair of tetralogy of Fallot consisting of pericardial grafting of the pulmonary outflow tract, closure of the ventriculoseptal defect, and primary closure of the patent ductus arteriosus. After an initially uneventful postoperative course, he developed sepsis of unknown cause on postoperative day 3 with subsequent respiratory compromise. The pulmonary findings were consistent with acute pulmonary edema. Extracorporeal membrane oxygenation (ECMO) was begun on postoperative day 8 for progressive respiratory failure unresponsive to medical management.

Bloody aspirate was first noted with endotracheal suctioning on the third day of ECMO bypass. Decreasing the rate of heparin infusion in combination with bronchial lavage using vasoconstrictive agents was initially successful. The bleeding progressed to frank endobronchial hemorrhage, necessitating high inspiratory pressures for chest expansion. Attempts at removal of the thrombus by suctioning and flexible bronchoscopy were unsuccessful.

Rigid therapeutic bronchoscopy was performed the following day with the patient continuously on ECMO. The procedure was performed in the cardiac surgery intensive care unit, under continuous monitoring and intravenous sedation. No attempt was made to ventilate the patient while the bronchoscopy was being performed.

Initial endoscopy revealed total obstruction at the level of the midtrachea by organized thrombus with clot extending into the segmental bronchi. Following successful removal, ventilatory pressures returned to normal. Repeat bronchoscopy was performed 4 days later for recurrent hemorrhage with findings of bilateral main stem bronchial obstruction due to thrombus (Fig 1). Removal of these endobronchial clots revealed a cast of the bronchial tree (Fig 2). A third and final bronchoscopy was performed 2 days later without evidence of active bleeding or thrombus.

Following an improvement in the chest radiographic and ventilatory parameters, the child was successfully taken off ECMO 2 days after the last bronchoscopy. Unfortunately, the child died less than 24 hours later of hyperkalemia associated with acute renal failure.

DISCUSSION

Currently, ECMO is indicated for the term or near-term infant (35 to 40 weeks' gestation) who fails maximal ventilatory and medical support and who, by institutional criteria, has only a 20% chance or less of survival.[1] Because of the need for systemic heparinization, hemorrhage remains the most frequent and most serious complication. At most ECMO centers, there is a clinical impression that hypoxemia severe enough to require transfusion prolongs weaning from bypass. For both these reasons, prevention of bleeding and its prompt control are important in ECMO patient management.[2]

Venoarterial bypass, as used in our patient, is

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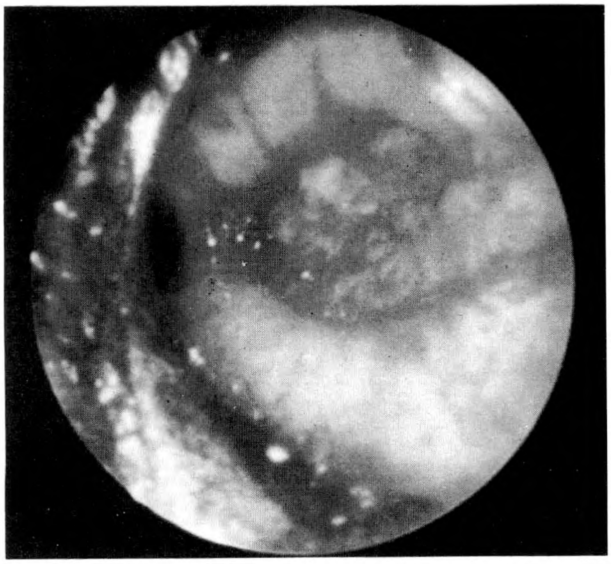

Fig 1. Endoscopic view of carina with thrombus occluding main stem bronchi.

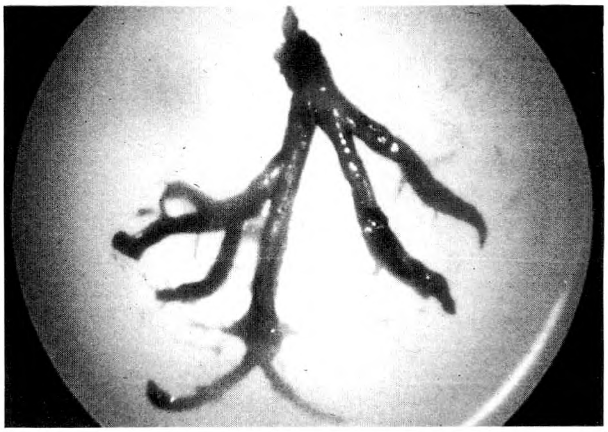

Fig 2. Thrombotic cast removed from right bronchial tree.

accomplished via cannulation of the ligated right internal jugular vein and common carotid artery (Fig 3). The newer technique of venovenous bypass involves cannulation of only the right internal jugular vein with a double-lumen catheter; blood is drained through one lumen and reinfused through the other. The carotid artery is thus spared and the higher flow rates required reduce the need for heparinization.

Bleeding at the surgical or cannulation sites is the most common hemorrhagic complication of ECMO. Surgical dissection with cautery and topical hemostatic agents such as fibrin glue are utilized to reduce the incidence of cannulation site bleeding.

Intracranial bleeding remains the most devastating hemorrhagic complication of ECMO, especially in premature infants.[3] Gastrointestinal, genitourinary, pleural, mediastinal, gingival, and nasal sites of bleeding have been described.[1,2,4,5]

The importance of continued ventilatory support and lung expansion during ECMO has been stressed by Keszler et al.[6] Prevention of atelectasis may improve lung recovery and help stimulate surfactant production. Maintaining optimal gas exchange in the lungs helps to shorten the length of time the patient is

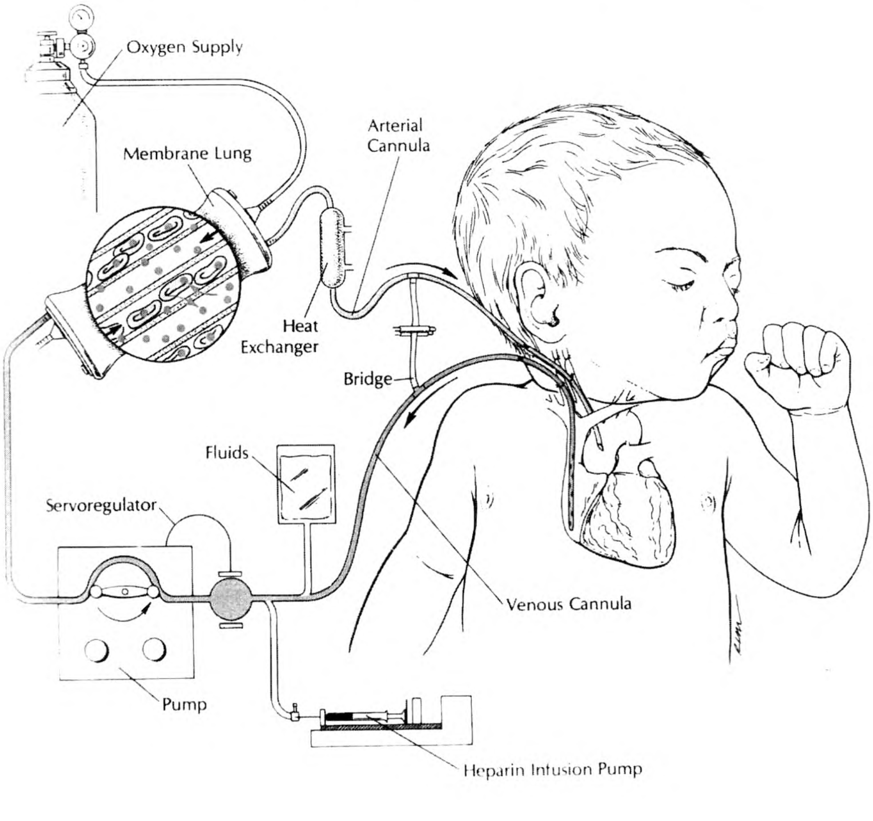

Fig 3. Extracorporeal membrane oxygenation by venoarterial route. Venovenous bypass utilizes single, double-lumen catheter placed in right internal jugular vein. (Reprinted by permission, Donn SM. ECMO indications and complications. Hosp Pract 1990;25:143-57. Illustration by Robert Margulies.)

dependent on ECMO, as well as providing a safety factor in case of mechanical complications that require interruption of the bypass circuit.

Sell et al[2] reported 5 cases of endobronchial bleeding in 25 patients receiving ECMO. Bleeding was felt to be due to the mucosal trauma of suctioning. The bleeding in all of these patients was controlled by phenylephrine (0.1%) lavage and increased positive end-expiratory pressure. Watson et al[7] describe a case of massive endobronchial bleeding, presumably due to endotracheal tube trauma, with successful conservative management.

In our patient, conservative measures were unsuccessful and rigid bronchoscopy was needed to clear the tracheobronchial tree of obstructive thrombi. The castlike nature and extent of the thrombus (Fig 2) would undoubtedly have been fatal if the endobronchial hemorrhage had occurred in another clinical setting.

Werkhaven and Holinger[8] reported 4 cases of tracheobronchial obstruction due to mucous casts. This unusual clinical condition presents an analogous situation, but the need to maintain adequate ventilation makes management of a mucous cast more challenging. In our case, the absence of ventilation was easily compensated for by ECMO, and rigid bronchoscopy was unencumbered by the need to provide ventilation. Ventilatory parameters improved after each bronchoscopic procedure, and eventually ECMO was no longer required.

Nonhemorrhagic airway complications have also been described. Following successful discontinuation of ECMO, G. Zalzal et al (unpublished observations) have found a 13.6% incidence of postextubation stridor, for which nearly half of these patients required flexible or direct laryngoscopic examination. Schumacher et al[9] have reported 5 cases (3.5% incidence) of true vocal cord paralysis following extubation. All were right-sided, transient, and felt to be due to local edema and irritation of either the recurrent and/or vagus nerves at the cannulation site.

There are currently over 100 centers world-wide performing ECMO. It is likely that as indications expand and technical limitations are resolved, the otolaryngologist will with increasing frequency be called upon to assist in the management of ECMO-related complications.

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COMPARISON OF RIGID AND FLEXIBLE ESOPHAGOSCOPY IN THE DIAGNOSIS OF ESOPHAGEAL DISEASE: DIAGNOSTIC ACCURACY, COMPLICATIONS, AND COST

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Rigid esophagoscopy has been used by otolaryngologists for evaluation of the esophagus for over 100 years. Few studies have examined the diagnostic accuracy of rigid esophagoscopy in patients with carcinoma of the head and neck. The goal of our study was to compare the diagnostic accuracy, complication rate, and costs of rigid esophagoscopy and flexible fiber-optic endoscopy in the evaluation of the esophagus in patients with head and neck carcinoma. We retrospectively reviewed the records of 195 patients with head and neck carcinoma who underwent both rigid esophagoscopy and flexible fiber-optic endoscopy within a 6-month period. We discovered 10 cases with discordant findings, of which 5 (50%) were esophageal carcinoma. The estimated cost was less for flexible endoscopy. No complications were reported in either procedure. Our study suggests that flexible fiber-optic endoscopy should replace rigid esophagoscopy in the evaluation of the esophagus in patients with head and neck carcinoma.

KEY WORDS — flexible fiber-optic endoscopy, head and neck carcinoma, panendoscopy, rigid esophagoscopy.

INTRODUCTION

Rigid esophagoscopy has been the technique utilized by otolaryngologists during the practice of "panendoscopy" for the evaluation of the upper aerodigestive tract. This procedure includes nasopharyngoscopy, laryngoscopy, bronchoscopy, and rigid esophagoscopy to 40 cm. Although the value of this technique as a whole has been investigated, the question of the diagnostic accuracy of rigid versus flexible fiber-optic esophagoscopy during this procedure has not been thoroughly evaluated.

Since the first flexible fiber-optic endoscope was constructed by Basil Hirschowitz[1] in 1957, the technique of flexible endoscopy has been the primary method employed by gastroenterologists for investigating patients with complaints involving the upper digestive tract. With the technical advances that followed the original design, gastroenterologists abandoned the rigid endoscope for the flexible version. It has proven easier to use, with fewer complications — in particular, fewer esophageal perforations.[2-6]

Our study suggests that with the availability of flexible fiber-optic endoscopy, use of rigid esophagoscopy in the technique of panendoscopy may be unwarranted. The purpose of this retrospective study was to compare the diagnostic accuracy, complication rate, and cost-effectiveness of rigid esophagoscopy employed in panendoscopy versus flexible endoscopy.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of all patients who underwent both rigid endoscopy and flexible endoscopy between 1989 and 1993. Patients were evaluated at the University of Illinois at Chicago Medical Center and the Westside Veterans Administration Medical Center. Patients were identified from The Endoscopy Database (formerly The American Society for Gastrointestinal Endoscopy) used by the Section of Digestive and Liver Diseases at the University of Illinois at Chicago.

All rigid endoscopic procedures were performed under general anesthesia. Flexible fiber-optic endoscopy was performed under conscious sedation induced by a combination of intravenous meperidine hydrochloride and midazolam. With both methods, the entire esophagus was examined to the gastroesophageal junction. Flexible endoscopy also included examination of the stomach and duodenum, as well as retroflexed views of the gastric cardia. Findings obtained by rigid endoscopy were compared to those of flexible endoscopy. A discordant finding was defined as any new lesion seen on flexible endoscopy not seen on the rigid esophagoscopy when

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TABLE 1. NUMBER AND TYPE OF ESOPHAGOSCOPIES PERFORMED FROM 1989 TO 1993

Procedure	*1989*	*1990*	*1991*	*1992*	*1993*	*Total (%)*
RE + TE	122	164	156	145	112	699
RE	43	71	30	40	16	200 (29%)
TE	79	93	126	105	96	499 (71%)
FE	13	47	62	43	30	195 (28%)

RE — rigid esophagoscopy, TE — triple endoscopy, FE — flexible endoscopy.

the procedures were performed within 6 months of each other.

To compare the total cost of each procedure, we calculated the fees for the following portions of the examination that make up the final cost of the procedure: physician's fee, room fee (ie, operating room or gastroenterology laboratory room), anesthesia fee (based on average time per case), and recovery room fee.

RESULTS

Between 1989 and 1993, 699 rigid esophagoscopies were performed by members of the Department of Otolaryngology–Head and Neck Surgery. Of these, 499 (71%) were performed as part of "triple" endoscopy or panendoscopy and 200 (29%) were performed as a single procedure. During this period, 195 (28%) of these patients also underwent flexible fiber-optic endoscopy within 6 months of rigid esophagoscopy. The total number of procedures is divided by type of procedure and year (Table 1).

The diagnostic findings of all 699 rigid esophagoscopies are seen in Table 2. The most common diagnosis was carcinoma of the head and neck (52%). Additional diagnoses included foreign body, esophageal carcinoma, and other miscellaneous findings. The examination findings were normal in 95 cases (14%). In the 369 (53%) patients with head and neck carcinomas found on rigid esophagoscopy, the most common type was glottic laryngeal carcinoma (115 or 31%). This was followed by supraglottic, floor of mouth, vocal cord, and nasopharyngeal carcinomas, occurring in 101 (27%), 82 (22%), 43 (12%), and 28 (8%) patients, respectively.

TABLE 2. DISORDERS DIAGNOSED ON RIGID ESOPHAGOSCOPY FROM 1989 TO 1993

Disorder	*1989*	*1990*	*1991*	*1992*	*1993*	*Total (%)*
H + N Ca	51	78	95	86	59	369 (53%)
Eso Ca	25	22	3	5	1	56 (8%)
FB	10	14	17	12	9	62 (9%)
Other	12	14	27	27	35	115 (16%)
Normal	24	36	13	12	10	95 (14%)

H + N Ca — head and neck cancer, Eso Ca — esophageal cancer, FB — foreign body, other — miscellaneous.

The records of 195 patients who underwent both rigid and flexible endoscopy from 1989 to 1993 were analyzed for discordant findings. We defined discordance as significant if lesions diagnosed on fiber-optic flexible endoscopy were not found on rigid esophagoscopy, and the procedures were performed within 6 months of each other. A total of 10 (5%) discordant findings were discovered. Of these, 5 were esophageal carcinomas. The other discordant findings were esophageal stricture, diverticulum, mucosal ring, esophagitis, and extrinsic compression of the esophagus. No complications were reported during either flexible fiber-optic endoscopy or rigid esophagoscopy.

The average costs of each portion of the procedure and their totals are seen in Table 3. Physicians' fees were comparable for both gastroenterologists and otolaryngologists performing the procedure. The fee for the operating room was 40% higher than the fee for the gastroenterology laboratory rooms. Because all rigid esophagoscopies require general anesthesia followed by time spent in the recovery room, fees for anesthesia and recovery averaged $400 and $110, respectively. Patients undergoing flexible endoscopy are not charged for separate anesthesia and recovery room fees. The total average cost for rigid esophagoscopy was 30% higher than that for flexible fiber-optic endoscopy.

DISCUSSION

Since the first reported use by Kussmaul in 1868, in the examination of a sword-swallower's esophagus,[7] rigid esophagoscopy has been the primary tool in the otolaryngological examination of the esophagus. Although the general principles of direct-vision examination have remained essentially unchanged, modern technology has afforded the physician the capability to examine the esophagus in an effective and relatively safe manner. In the climate of advancing medical technology, the role of rigid esophagoscopy is uncertain. The purpose of our investigation was to evaluate the diagnostic accuracy, complication rate, and cost of rigid esophagoscopic examination.

TABLE 3. COST COMPARISON BETWEEN FLEXIBLE ENDOSCOPY AND RIGID ESOPHAGOSCOPY

Fee	*Rigid Esophagoscopy*	*Flexible Endoscopy*
Physician fee	$ 600	$ 650
Anesthesia fee	400	0
Operating room fee	835	500
Recovery room fee	110	0
Total fee	$1,945	$1,150

In the earliest reported comparison of rigid versus flexible esophagoscopy, in 1968, Zimmon and Tesler[8] compared the accuracy of fiber-optic and rigid esophagoscopy in the diagnosis of esophageal varices. Their results were based on objective findings of the two endoscopists. Of 51 endoscopies performed, fiber-optic esophagoscopy overlooked esophageal varices in 14 of these cases in which rigid esophagoscopy had identified esophageal varices. The discrepancy between these two methods was magnified in patients with smaller varices (grades I and II) as compared to larger varices (grades III and IV). The investigators attribute this difference to increased peristalsis caused by the air insufflation required during fiber-optic examination, which obliterated smaller varices. During the study, patients underwent both procedures in succession under intravenous sedation with 50 mg of meperidine hydrochloride and 1.2 mg of atropine sulfate. Of interest, general anesthesia, used today for rigid esophagoscopy, was not employed. No complications were reported with either method. When questioned about comfort, 28 of the 36 (78%) patients preferred the fiber-optic examination over rigid esophagoscopy. Furthermore, despite the superior results of the rigid esophagoscope, the endoscopists reported superb clarity, ease of passage, and comfort in using the then-new fiber-optic endoscope. The major flaw in this study was the large amount of observer error reported (17%), which the authors commented could have been decreased by further endoscopic experience.

Several studies have questioned the diagnostic accuracy of flexible endoscopy versus rigid esophagoscopy regarding the quality of biopsy material obtained during examination.[9-12] Cheung et al,[13] in 1988, compared findings of esophagoscopy and bronchoscopy using both rigid and flexible instruments in the evaluation of esophageal cancer patients for surgery. In this study, 71 patients underwent both examinations. In all cases, the tumor was visualized by both procedures. The histologic diagnosis of malignancy was confirmed by endoscopic biopsy during flexible endoscopy in all patients. In addition, a second tumor nodule was found in the distal esophagus in 2 patients during flexible endoscopy that was not detected by rigid esophagoscopy.

Additional studies have examined the use of rigid esophagoscopy in diseases of the aerodigestive tract. In a retrospective review of 294 rigid esophagoscopies performed from 1983 to 1990 at the Hospital of University of Pennsylvania, Bacon and Hendrix[14] examined the indications, advantages, and risks of open tube (rigid) esophagoscopy. The most common indication for rigid esophagoscopic examination was evaluation of head and neck oncologic patients for a second primary tumor, including esophageal carcinoma. In their review, the authors reported 2 of 141 (1.4%) patients to have a second esophageal tumor discovered by rigid esophagoscopy. Multiple head and neck tumors were found in 12 of 141 patients (8.5%). The endoscopists reported an incomplete examination (ie, unable to reach the gastroesophageal junction) in 45 (15%) of the 294 rigid esophagoscopies performed. The most common causes included body habitus, cervical osteoarthritis, stricture, and obstructing masses. Minor complications, such as mucosal abrasion and postesophagoscopy fever, were seen in 2.7% and 4%, respectively. Rigid esophagoscopy was complicated by esophageal perforation in 3 patients. All 3 had undergone dilation of cervical strictures. In 2 patients, the stricture was due to a carcinoma, while in the third patient, the stricture was related to postirradiation and postoperative changes. One of the 3 patients died of complications arising from the perforation and subsequent drainage attempts. The overall perforation and mortality rates were 1% and 0.3%, respectively.

The use of flexible endoscopy is not a novel technique to the otolaryngologist. In 1985, Batch[15] reviewed 53 patients who underwent flexible endoscopy performed by an otolaryngologist for the evaluation of pharyngeal symptoms. The two most common diagnoses were cricopharyngeal spasm (19 patients) and gastroesophageal reflux (24 cases). Of the 53 patients, 6 underwent both types of examinations. In 3 of the cases, flexible fiber-optic endoscopy identified lower esophageal disease not seen by rigid endoscopy under general anesthesia. In these cases, the rigid endoscopic examination diagnosed laryngitis and pharyngitis, but failed to diagnose severe gastroesophageal reflux. No cases of gastrointestinal malignancies were identified on either type of examination. In the review by Cheung et al,[13] flexible endoscopy detected 2 carcinomas of the lower esophagus missed by rigid esophagoscopy. In our retrospective review, of the 10 lesions seen on flexible endoscopy, 7 were found in the lower esophagus. This further reinforces the theory that the majority of lesions missed by rigid endoscopy occur in the lower portion of the esophagus.

Although the greater diagnostic accuracy of the flexible endoscope over the rigid type in lesions involving the lower esophagus is apparent, superiority in the examination of the upper esophagus is not as evident.[16] In the study by Batch,[15] only 1 lesion seen by rigid examination was missed on flexible endoscopy. Of importance, of the 10 discordant lesions seen in our review, rigid esophagoscopy missed

3 lesions of the upper esophagus; this finding suggests that flexible esophagoscopy can detect lesions of the upper esophagus not seen on rigid examination. With proper technique using careful, slow withdrawal from the upper esophagus, flexible endoscopy is an adequate diagnostic tool in evaluating upper esophageal lesions.

Although not the tool of choice for examination of the larynx and pharynx, flexible fiber-optic endoscopy may be helpful in detecting lesions of the larynx, including laryngeal carcinoma. In a study by Lehman et al,[17] in 1982, screening laryngeal-pharyngeal examinations were performed during 1,120 flexible fiber-optic esophagogastroduodenoscopies. In their series of upper endoscopic examinations, the authors were able to visualize the larynx and pharynx in 82.4% and 78%, respectively. A total of 39 laryngeal lesions were detected. Most lesions were chronic laryngitis or vocal cord contact granuloma. Two patients were found to have leukoplakia of the vocal cord, a known risk factor for carcinoma. Of interest, 1 of the 2 patients subsequently developed squamous cell carcinoma of the vocal cord.

One clinical situation in which rigid endoscopy is considered superior to flexible endoscopy is in the visualization and removal of foreign bodies from the esophagus.[18,19] This is explained by the fact that most foreign body impaction occurs in the cervical esophagus, an area felt to be better examined with a rigid instrument.[20] Hawkins,[21] in 1990, reported the successful management of blunt foreign bodies from the esophagus in 231 patients by means of rigid esophagoscopy with no reported perforations or deaths. Other studies have shown a perforation risk between 0.25% and 0.6%.[22-24]

Although no complications were reported in our study, the safety of flexible endoscopy versus rigid endoscopy is a concern. In a study of Silvis et al[3] in 1976, the total complication rate for fiber-optic endoscopy was 1.3 per 1,000 cases for over 210,000 investigations, with a mortality rate of approximately 0.007%. Perforations with both the rigid and flexible endoscopies are well documented,[4] although accidents of this nature are less likely to occur with the flexible instrument.[5,6,25] Use of the rigid instrument is particularly difficult in elderly patients with cervical spine arthropathy[26] or thick-necked patients with a full set of teeth. In addition, many patients who are considered unacceptable risks for general anesthesia would not be good candidates for rigid endoscopy. These patients may be evaluated relatively safely with flexible endoscopy.

In addition to relatively safe evaluation of the esophagus in patients with carcinoma of the head and neck, another benefit of flexible endoscopy is the capability for insertion of a percutaneous endoscopic gastrostomy. Gibson et al[27] demonstrated relatively safe placement of these in patients with head and neck carcinoma. Complications occurred in 5% of patients with head and neck tumors, compared to 14% in all other patients. In patients with head and neck carcinoma, factors contributing to a lower complication rate included younger age, fewer complicating medical problems, and better nutritional status.

Finally, in our study, a disturbing trend of missed esophageal malignancies was seen in cases of discordant findings. Out of the 10 discordant cases, 50% were esophageal cancers. This is an alarming finding that suggests small tumors may be missed on routine rigid esophagoscopy. The most likely explanation of this finding is that the esophagus is more completely visualized with the flexible endoscope. Both the continuous insufflation of air and the flexible tip favor recognition of small lesions by the flexible instrument. With the flexible tip, straight-on inspection improves the diagnostic yield. In the only other study comparing rigid versus flexible endoscopy in diagnosis, Batch[15] studied only 6 patients who underwent both examinations. Of the 3 discordant findings, none were esophageal cancers. These numbers are significantly smaller and may be of no statistical significance when compared with our data.

CONCLUSION

Our study confirms that a discrepancy exists between findings in patients who have undergone both rigid and flexible endoscopy for evaluation of the esophagus. Our discordance rate of 6.3% suggests flexible esophagoscopy is a better diagnostic tool than rigid endoscopy. The cost comparison between the procedures favors the less expensive flexible fiber-optic endoscopy, mostly because of the requirement for general anesthesia in rigid esophagoscopy. In the current environment of emphasis on efficiency, safety, and cost containment, our study would suggest that flexible fiber-optic endoscopy should replace rigid endoscopy for the evaluation of esophageal disease.

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AERODIGESTIVE TRACT FOREIGN BODIES IN THE OLDER CHILD AND ADOLESCENT

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This study was undertaken in order to establish the incidence of aerodigestive tract foreign body accidents among older children and adolescents, and to investigate the circumstances surrounding these events. A review of patients treated over a 5-year period identified 367 children from whom aerodigestive tract foreign bodies were removed. Seventeen percent of these patients were 5 years of age or older. Among these children, 88% aspirated nonfood items, half of which were school supplies; 78% of the group 5 years old and under aspirated food items. Among older children with esophageal foreign bodies, 31% had food impactions, compared with 7% in the younger group; 70% of these children had a history of some anatomic abnormality of the esophagus. These data suggest that older children and adolescents represent a distinct group of patients at risk for foreign body accidents. Pediatricians and parents of children in this age group should discourage the practice of using the oral cavity as a repository for school supplies, and should stress the need for adequate preparation and mastication of food, particularly among children with esophageal abnormalities.

KEY WORDS — adolescent, airway, child, esophagus, foreign body.

INTRODUCTION

Despite continued advances in first aid and endoscopic technology, foreign bodies of the pediatric aerodigestive tract remain a diagnostic and therapeutic challenge. Foreign bodies of long standing and those causing significant tissue reaction may also be a source of considerable morbidity.

Within the pediatric age group, most victims of foreign body accidents are older infants and toddlers. These children have not yet developed a full posterior dentition, and neuromuscular mechanisms for swallowing and airway protection are not fully mature. In addition, children of this age have a tendency to explore their world using their mouths. As a result, parents are routinely cautioned by their pediatricians and family practitioners to avoid feeding these children such foods as nuts and seeds, and to keep potentially ingestible objects out their reach.

Foreign body accidents among older children and adolescents are less easily explained. School-age children are generally quite capable of mastication and deglutition, and can identify items that are acceptable for oral ingestion. Nevertheless, nearly one in five victims of foreign body aspiration among children is over the age of 5,[1-12] and esophageal foreign bodies in this age group are also not infrequently seen.

This study was undertaken in order to characterize foreign body accidents among older children and adolescents. Identification of children at risk for these events is of paramount importance to the continued success of prevention programs.

METHODS AND MATERIALS

Records of patients with suspected aerodigestive tract foreign bodies treated at the Children's Memorial Medical Center, Chicago, during the 5-year period from January 1989 to December 1993 were retrospectively reviewed. Charts were selected on the basis of a computer search of cases that were ICD-9 coded for "foreign body" and one or more of the following anatomic sites: pharynx, larynx, trachea, bronchus, or esophagus. Patients who did not undergo an endoscopic procedure were omitted from the study.

Data collection was based on emergency room records, admission history and physical examination, anesthesia evaluation, and operative and postoperative notes. The following information was recorded: age and sex of patient, location of foreign body, type of foreign body, witnessed or unwitnessed event, symptoms, radiographic findings, anatomic abnormalities noted at endoscopy, and complications.

Children over the age of 5 were assigned to the

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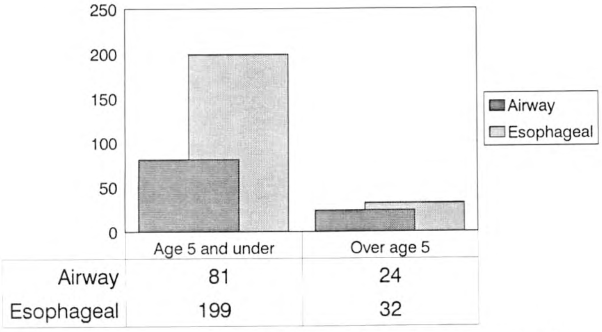

Fig 1. Airway versus esophageal foreign bodies distributed by patient age.

TABLE 1. AIRWAY FOREIGN BODIES BY LOCATION

Location	*No. of Foreign Bodies*	*% of Foreign Bodies*
Pharynx	9	8.2
Larynx	4	3.6
Trachea	7	6.4
Right main bronchus	40	36.4
Right segmental bronchus	8	7.3
Left main bronchus	36	32.7
Left segmental bronchus	6	5.5

study group of older children and adolescents. Children age 5 and under constituted the group for comparison.

RESULTS

Our review identified 367 patients who underwent endoscopy for a suspected aerodigestive tract foreign body. Rigid bronchoscopy was performed in 135 patients (37%), and rigid esophagoscopy in 232 (63%). Three hundred six patients (83%) were age 5 or under, and 61 (17%) were over age 5. Among the younger children, esophageal foreign bodies outnumbered airway foreign bodies by a 2.5 to 1 margin, and boys outnumbered girls by a margin of 1.7 to 1. In the older group, esophageal foreign bodies were more common by a margin of 1.3 to 1, and boys outnumbered girls by 1.5 to 1 (Fig 1).

Among the 135 patients undergoing bronchoscopy, no foreign body was identified in 30 patients, yielding a negative bronchoscopy rate of 22%. The age distribution of the remaining 105 patients, shown in Fig 2, was bimodal, with peaks between 1 and 2 years of age, and between 10 and 11 years of age. Among the 81 patients (77%) who were age 5 and under, the median age was 1.6 years, while the median age of the group over age 5 (24 patients; 23%) was 10.3 years.

The distribution of airway foreign bodies is shown in Table 1. Right bronchial foreign bodies accounted for 44% of the total, while left bronchial foreign bodies were present in 38%. Pharyngeal, laryngeal, and tracheal foreign bodies were present in 8%, 4%, and 6%, respectively. The 105 patients had a total of 110 foreign bodies, with two foreign bodies found in each of five patients.

The types of airway foreign bodies identified are depicted graphically in Figs 3 and 4. Overall, 64% of the airway foreign bodies were food items, with nuts and seeds alone accounting for 50% of the total. Among children 5 years of age and younger, food items were present in 79%, and nonfood items in 15% (Fig 3). In contrast, children over age 5 were far less likely to aspirate food items (12%) than nonfood items (88%). In the older age group, pen parts accounted for 25% of the objects found, and tacks, pins, and paper clips for an additional 25% (Fig 4).

Aspiration events were witnessed or reported by the patient in 75% of the cases in the younger age group and in 83% of the older children. The mean time to presentation was 11.4 days in the 5-and-under group, and 2.6 days in the group over 5. Symptoms were not significantly different between the two groups, with cough (64%) and wheezing (48%) found most commonly (Table 2).

Radiographic findings in the airway patients are summarized in Table 3. Radiopaque foreign bodies were more common in the group over age 5 (25% versus 5%). Obstructive emphysema and mediastinal shift were more common in the younger group (44%

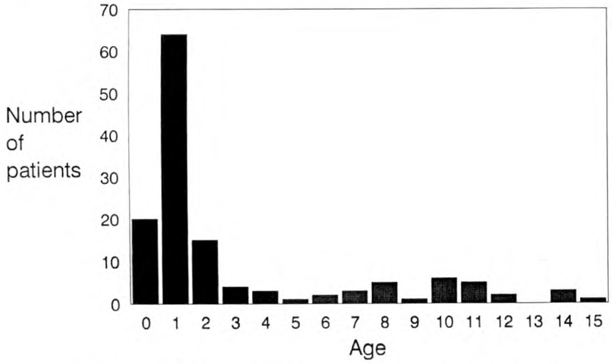

Fig 2. Airway foreign bodies distributed by patient age.

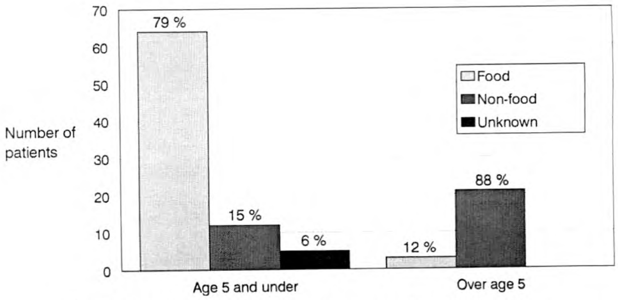

Fig 3. Food versus nonfood airway foreign bodies.

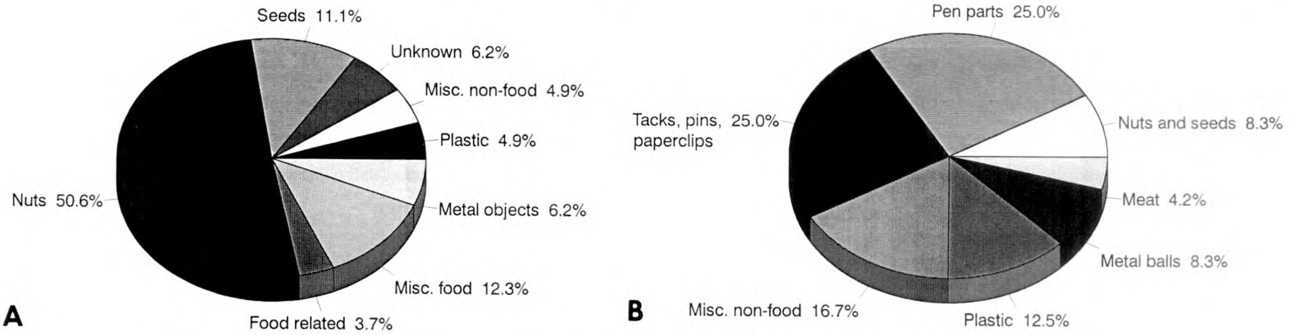

Fig 4. Airway foreign bodies distributed by type. A) Patients age 5 and under. B) Patients over age 5.

versus 13%).

Among the 232 patients undergoing esophagoscopy, no foreign body was identified in 1 patient, yielding a negative esophagoscopy rate of 0.4%. The age distribution of the remaining 231 patients, shown in Fig 5, was asymptotic, beginning with children under age 1. Of the 199 patients (86%) who were age 5 and under, the median age was 1.3 years, while the median age of the group over age 5 (32 patients; 14%) was 7.6 years.

The types of esophageal foreign bodies identified are depicted graphically in Fig 6. Coins were the most common object found in both groups, accounting for 76% of the items in the younger patients, and 53% of the items in the group over 5. Among children 5 years of age and younger, food items were present in 7%; in contrast, children over age 5 were more likely to impact food items (31%) (Table 4).

Esophageal impaction was witnessed or reported by the patient in 61% of the cases in the younger age group and in 78% of the older children. The mean time to presentation was 1.4 days in the 5-and-under group, and less than 1 day in the group over 5. Symptoms were not significantly different between the two groups, with vomiting (33%) and dysphagia (24%) found most commonly (Table 5). Radiopaque esophageal foreign bodies were present in 88% of children 5 and under, and in 59% of children over 5.

TABLE 2. SIGNS AND SYMPTOMS OF AIRWAY FOREIGN BODIES

	Age 5 and Under (%)	*Over Age 5 (%)*
Witnessed event	75	83
Cough	65	58
Wheezing (history)	49	33
Pneumonia (history)	9	4
Fever	25	8
Decreased breath sounds	40	42
Wheezing on exertion	42	29
Stridor	12	4

Mean time to presentation was 11.4 days in younger group, and 2.5 days in older group.

Of the 24 cases of food impaction (10% of total), 19 (79%) were associated with a history of tracheoesophageal fistula, congenital esophageal atresia, or acquired esophageal stricture. While such cases accounted for only 6% of the esophageal foreign bodies in the younger group, patients with anatomic abnormalities of the esophagus represented 22% of the group over age 5.

DISCUSSION

Recent reviews of foreign body aspiration in children estimate that nearly 20% of these accidents occur in older children and adolescents. In our series, 23% of airway foreign bodies and 14% of esophageal foreign bodies were removed from children in this age group. Since these are generally children who have the mental capacity to select items appropriate for consumption and the physical capacity to thoroughly chew and swallow them, it is important to determine the circumstances under which these accidents occur.

In most cases, esophageal foreign bodies occur when a deliberate attempt at ingestion of an object results in impaction in the esophagus. Foreign bodies of the airway, on the other hand, are rarely inhaled intentionally, and are more appropriately regarded as "accidents." It is therefore not surprising that among older children, who are less likely to intentionally ingest objects inappropriate for consumption, the ratio of esophageal foreign bodies to airway foreign bodies was substantially lower than that among

TABLE 3. RADIOGRAPHIC FINDINGS OF AIRWAY FOREIGN BODIES

	Age 5 and Under (%)	*Over Age 5 (%)*
Obstructive emphysema or mediastinal shift	44	13
Pneumonia	7	4
Atelectasis	7	0
Radiopaque foreign body	5	25

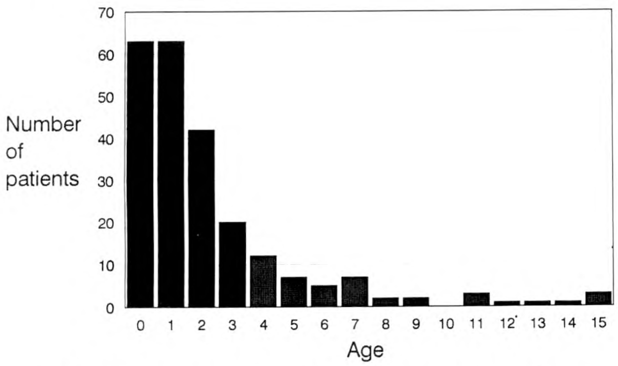

Fig 5. Esophageal foreign bodies distributed by patient age.

younger patients. The larger size of the laryngeal inlet in older children may also have contributed to the denominator in these ratios.

Among younger children with airway foreign bodies, the vast majority of objects removed were food items, usually nuts or seeds. This result clearly demonstrates that most foreign body accidents result not from unsupervised exploration by children, but from inadequate parental control of access to commonly aspirated food items.

The data from cases involving older children with airway foreign bodies suggest that immature masticatory skills and oral exploration have little bearing on aspiration events in this age group. If this were the case, one would have expected the patients in this group to have been clustered near age 5, and the median age to have been similar to that of 7.6 years found among the older children with esophageal foreign bodies. In fact, the bimodal age distribution of children with airway foreign bodies had its second peak between ages 10 and 11, and the median age among the older children was 10.3 years. Although the number of patients in this age group was small, this age distribution has also been observed by other authors.[4,13,14]

Older children also tended to aspirate nonfood objects far more frequently than younger children, and about half of these objects were pen parts, pins, tacks, and paper clips. It might therefore be postulated that children in the latter half of grade school who have become familiar with school supplies place these objects in their mouths either as part of a game (ie, using push pins as "blow darts") or to use the oral cavity as a temporary repository while the hands are otherwise occupied (ie, holding tacks in the mouth while mounting items on a bulletin board, or holding a pen cap in the mouth while writing with the pen). The object is then easily inhaled by accident when the patient is startled or distracted. Alternatively, aspiration may occur while a child is running or playing with an object in his or her mouth.

TABLE 4. FOOD VERSUS NONFOOD ESOPHAGEAL FOREIGN BODIES

	Food	*Nonfood*	*Unknown*	*None*
Age 5 and under	14	182	3	1
Over age 5	10	22	0	0

Although signs and symptoms of foreign body aspiration were similar between the groups, older patients tended to present earlier and had a slightly higher percentage of witnessed events. Frequently, parents who witness an aspiration event in a young child will downplay the significance of the preceding coughing episode since the child is initially asymptomatic. Older children, on the other hand, can often describe the event more accurately, leading to earlier medical intervention. The higher incidence of obstructive emphysema and mediastinal shift in the younger group may have resulted from increased airway inflammation due to the longer time to presentation, or from more severe obstruction due to the smaller size of the airway. The high percentage of radiopaque foreign bodies among older children was consistent with their higher rate of aspiration of nonfood objects.

Signs and symptoms in patients with esophageal foreign bodies were very similar in the two groups studied. The age distribution of children with esophageal foreign bodies demonstrated a decreasing inci-

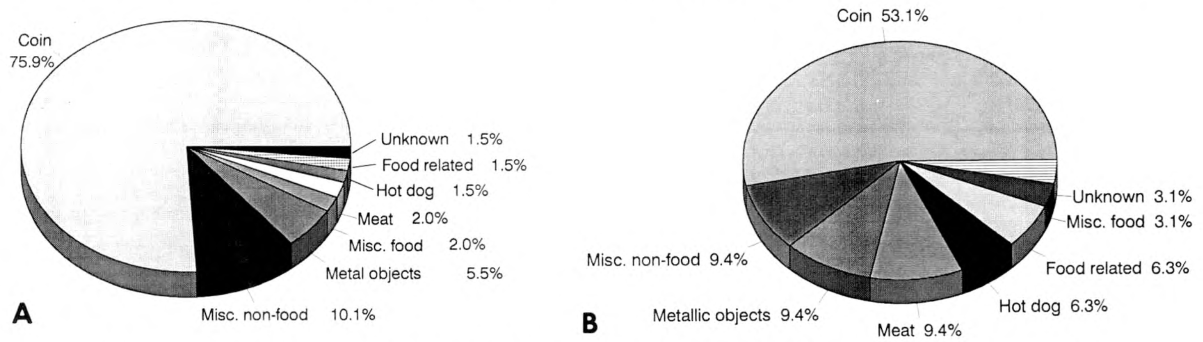

Fig 6. Esophageal foreign bodies distributed by type. A) Patients age 5 and under. B) Patients over age 5.

TABLE 5. SIGNS AND SYMPTOMS OF ESOPHAGEAL FOREIGN BODIES

	Age 5 and Under (%)	*Over Age 5 (%)*
Witnessed event	61	78
Cough	31	0
Wheezing (history)	7	0
Dysphagia	23	31
Odynophagia	7	25
Anorexia	13	0
Vomiting	35	22
Fever	14	0
Wheezing on exertion	7	0
Stridor	5	0

Mean time to presentation was 1.37 days in younger group, and 0.04 days in older group.

dence with age, reflecting a lower rate of inappropriate ingestion among older children. Food impaction, therefore, accounted for a substantially higher percentage of cases among the older children than in the younger age group. In both groups, anatomic abnormalities of the esophagus were encountered in the vast majority of food impactions, and were responsible for nearly one quarter of all cases in the older group.

The most effective treatment of foreign body accidents is their prevention. Just as pediatricians use well-child visits to advise parents of infants and toddlers not to feed their children nuts and seeds, they should similarly educate older children and their parents on the risks of storing school supplies and other objects in their mouths. Older children with anatomic abnormalities of the esophagus must additionally be taught to prepare and masticate their food carefully as they become more independent feeders.

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INTRALESIONAL VINBLASTINE FOR TREATING AIDS-ASSOCIATED KAPOSI'S SARCOMA OF THE OROPHARYNX AND LARYNX

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Kaposi's sarcoma (KS), the most frequent malignant neoplasm associated with acquired immunodeficiency syndrome, often involves the oropharynx and larynx. This study evaluated the efficacy of intralesional vinblastine sulfate injection in oropharyngeal and laryngeal KS. Twenty-four human immunodeficiency virus–positive patients with a total of 26 KS lesions were treated with injections of 0.1- or 0.2-mg/mL vinblastine sulfate solution. Subsequent injections were administered at 4- to 5-week intervals if necessary until the lesions resolved or stabilized. Complete regression was achieved in 16 lesions (62%), 20% to 50% reduction in 4 lesions (15%), and less than 20% reduction in 3 lesions (12%). Two lesions (8%) did not respond, and 1 (4%) grew despite the injections. Thirteen patients experienced no adverse effects. Eleven patients reported pain not relieved by acetaminophen; 5 of these 11 also had ulceration secondary to the injection. Both pain and ulceration were self-limiting. We conclude that vinblastine injection is a viable option for treatment of oropharyngeal and laryngeal KS lesions.

KEY WORDS — acquired immunodeficiency syndrome, Kaposi's sarcoma, vinblastine.

INTRODUCTION

Kaposi's sarcoma (KS) is the most frequent malignant neoplasm in acquired immunodeficiency syndrome (AIDS).[1] The value of intralesional vinblastine sulfate in the treatment of cutaneous KS lesions has been well established. In fact, intralesional antineoplastic agents have been used in treating KS lesions since the 1960s.[2] Vinblastine's role in the management of oral, pharyngeal, and laryngeal KS, however, has not been elucidated. Kaposi's sarcoma commonly develops in these sites, sometimes as the presenting symptom of AIDS. In addition, laryngeal and pharyngeal KS can cause far more significant symptoms than cutaneous lesions because of the potential for obstruction of the aerodigestive tract. Early control of the lesions may therefore be warranted.

This study was done to evaluate the efficacy of intralesional vinblastine injection in treating oropharyngeal and laryngeal KS. The primary objective of treatment was palliation.

MATERIALS AND METHODS

Patients positive for human immunodeficiency virus (HIV), with biopsy-proven KS lesions of the oral cavity, pharynx, or larynx, who had not undergone radiotherapy or systemic chemotherapy were included in the study.

Vinblastine sulfate was administered in a solution of either 0.1 or 0.2 mg/mL, by means of a 1-mL allergy syringe with a nondetachable 27-gauge needle. We preferred to use the 0.2-mg/mL solution, reverting to 0.1 mg/mL if side effects such as pain or ulceration occurred. The dosage used was 0.1 mL/cm^2 of lesion surface area. Multiple injections were made depending on the size of the lesion. The solution was injected superficially, resulting in blanching of the lesion. Laryngeal and pharyngeal lesions were injected under direct visualization and general anesthesia. A 7-inch, 22-gauge spinal needle was used to perform the injections.

The diameter of a lesion to be treated was estimated before injection. Patients were then treated approximately every 30 days until the tumor was completely flat. Typically, patients were examined and the sizes of their lesions estimated 12 to 16 days after injection. If required, injections were repeated 28 to 34 days after the previous injection. Vinblastine treatments were discontinued if the lesion resolved completely or stabilized in terms of size or pigmentation. The duration of response was recorded, and the use of analgesics was monitored as a guide to the severity of postinjection pain.

RESULTS

We treated a total of 26 lesions in 24 patients. Their

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ages ranged from 26 to 50 years, and all were men. The most common site of involvement was the palate (9 lesions), followed by the larynx (6), pharynx (5), gingiva (3), tongue (2), and buccal mucosa (1). The sizes of the presenting lesions ranged from 0.1 to 9 cm in diameter; most (17) were between 1 and 2 cm in diameter.

Thirteen patients (54%) tolerated all the injections well with no morbidity. Six patients (25%) reported pain not relieved by acetaminophen, and 5 patients (21%) had ulceration and pain secondary to the injection. Both pain and ulceration were self-limiting. All ulcers healed within 2 weeks, except for 1 case in which the ulcer required 4 weeks to heal. Seven patients were switched to the 0.1-mg/mL concentration because of intolerance of the 0.2-mg/mL concentration. No patients developed detectable edema.

The numbers of injections required were as follows: 1 injection in 10 patients, 2 in 2, 3 in 4, 4 in 5, 5 in 2, and 9 in 1 (three injections in each of three lesions).

One patient of particular interest presented with stridor due to multiple laryngeal lesions in the epiglottis, arytenoid cartilage, and base of the tongue. This patient (our only patient with multiple lesions treated) required tracheostomy at the time of the vinblastine injection. He received a total of 3 injections per lesion. While the response was satisfactory in the epiglottic and arytenoid lesions, the lesion at the base of the tongue remained stable, showing no signs of regression or growth. The patient did well over a 6-month period and tolerated decannulation. However, he died of other causes 1 year after the initial injection.

Follow-up ranged from 10 months to 3$^1/_2$ years, during which time no patients received adjuvant therapy for KS. Complete regression, defined as a final lesion size of 0 to 0.5 cm in diameter, was achieved in 16 lesions (62%). A partial response, defined as a reduction of 20% to 50% in diameter, occurred in 4 lesions (15%). An incomplete response (reduction of less than 20%) occurred in 3 lesions (12%). Two lesions (8%) did not respond, and growth was noted in spite of injections in 1 lesion (4%). Recurrence after complete response occurred in 3 patients (13% of lesions) during the limited follow-up period. Two of these patients underwent repeated injection and showed a good response; the third was not considered a candidate for repeated injection because he developed multiple lesions.

DISCUSSION

Kaposi's sarcoma is a tumor of endothelial or spindle cell origin. No etiologic agent has yet been identified, but recent evidence suggests that a herpesvirus may be a cofactor in its development.[3] Oropharyngeal KS may be the first sign of HIV infection or may develop during the course of the illness. It most often involves the palate, but may also involve the gingiva, dorsum of the tongue, or other oral sites. Early lesions present as red to reddish blue macules with indistinct margins, and progress to elevated bluish purple nodules.[4] Intraoral lesions may present with pain, bleeding, and difficulty in speech and swallowing.[5] Laryngeal or pharyngeal lesions may present with dysphagia or signs of upper airway obstruction.

Although the prevalence of HIV infection is increasing, the prevalence of HIV-associated KS is decreasing.[6,7] Currently, it is estimated that 10% to 20% of patients with AIDS develop KS, and that oral lesions occur in approximately half of these cases of KS.[4,5] Non–AIDS-related KS, on the other hand, is a rare lesion in North America, accounting for 0.02% to 0.06% of all malignancies.[8,9]

Patients with HIV and KS seek treatment of individual lesions for reasons that include pain, edema, functional disability, and cosmesis. Many lesions are asymptomatic when diagnosed early, but symptoms are likely to develop if growth is not controlled. Existing treatment modalities include local or systemic therapy and immunotherapy. Local treatment includes radiotherapy, cryotherapy, laser therapy, photodynamic therapy, topical tretinoin gel, cimetidine, surgical excision, and intralesional vinblastine. Systemic chemotherapy usually consists of interferon-α, vinblastine and vincristine sulfate, vincristine alone, or a combination of doxorubicin hydrochloride, bleomycin sulfate, and vincristine. The multitude of treatments used attests to the lack of superiority of any one over the others.

Troublesome mucositis is a well-known complication of radiotherapy of the head and neck. Further, only 20% of lesions regress completely; even then, recurrence within 4 to 6 months is common.[10,11] Chemotherapy with doxorubicin, bleomycin, and vincristine in various combinations achieves partial response rates ranging from 72% to 88%. Complete remission occurs in only 30% of cases, and the adverse effects of chemotherapeutic agents are well known. Further, chemotherapy may help control disease, but it does not alter the prognosis. Surgical excision is appropriate for lesions that are localized and accessible; diffuse, extensive, or multiple lesions are not amenable to excision. Laser excision is useful for exophytic lesions. Immunotherapy has been associated with fatigue, myalgia, asthenia, neutropenia, and thrombocytopenia.

Scott and Vought[2] in 1966 first reported their experience with systemic chemotherapy in patients with KS using vinblastine with and without vincristine. Klein[12] in 1968 successfully used intralesional vinblastine injection, concluding that local administration of antitumor agents permitted higher concentrations to be achieved in the lesions with a relatively small amount of drug. In 1980, Klein et al[13] again reported successful use of intralesional vinblastine therapy for cutaneous KS. Since then, the technique has become more common.

Isolated KS lesions are most amenable to intralesional vinblastine treatment. Conant et al[14] recommend local therapy for KS when the following criteria are fulfilled: 1) a "manageable" number of lesions involving the integument, 2) an "acceptable" rate of new lesion formation, and 3) no evidence of significant or increasing internal lesions; or 4) troublesome individual lesions in patients with progressive KS being treated with aggressive systemic therapy.

The toxicity associated with intralesional vinblastine in our study has for the most part been local, mild, and transient. Administration is effective and economical compared with other types of treatment, easily performed, and generally well tolerated. While the use of this modality has been considered optional but not essential in the management of cutaneous and oral lesions, in laryngeal KS it may prevent life-threatening complications associated with airway compromise. The lack of any significant edema resulting from the injection of vinblastine makes it an ideal agent in the palliative treatment of small to moderate-sized lesions of the larynx and oropharynx.

CONCLUSION

In this study, treatment of oropharyngeal and laryngeal KS lesions with vinblastine injection resulted in minimal morbidity and good response in the majority of patients. This experience parallels the reported results of vinblastine treatment of cutaneous lesions. Intralesional vinblastine should be considered a valuable option for oropharyngeal and laryngeal KS lesions if treatment is planned.

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EVALUATION OF HER-2/NEU (C-ERBB-2) ONCOGENE EXPRESSION IN WHOLE ORGAN SECTIONS OF SUPRAGLOTTIC SQUAMOUS CELL CARCINOMA

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Adequate pathologic material and careful clinical follow-up are prerequisites for the analysis of the expression of particular oncogenic proteins that are prognostically important in squamous cell carcinoma of the larynx. The Gabriel Tucker, Jr, Collection of 150 whole organ specimens allows for the potential immunohistochemical study of the entire tumor. Sections from 32 supraglottic carcinomas were studied immunohistochemically for the presence of HER-2/neu (c-erbB-2) oncogene expression. Long-term follow-up data were available in all cases to assist in determining the prognostic significance of the specified oncogene in supraglottic squamous cell carcinoma. Our study revealed that joint presentation of immune staining for c-erbB-2 and positive lymph node status was significantly associated with distant metastasis ($p = .00760$).

KEY WORDS — c-erbB-2, distant metastases, HER-2/neu, larynx cancer, lymph node metastases, oncogene, squamous cell carcinoma, supraglottic larynx cancer.

INTRODUCTION

The large North American series of surgically managed squamous cell carcinomas of the supraglottic larynx have consistently reported a local control of 95% or better.[1,2] Although a more aggressive surgical approach to regional lymph node metastases in the neck, with increased utilization of modified neck dissection at the time of primary surgical therapy, has yielded improved control rates in the neck, certain patients continue to succumb to distant metastatic disease.[3] The presently available prognostic indicators have failed to consistently identify the patients at high risk for late distant failure.[4]

In an effort to identify factors involved in tumorigenesis of squamous cell carcinomas in various sites, a number of studies have focused on the activation of the cellular proto-oncogene c-erbB-2.[5-8] C-erbB-2 is a 185,000 d epidermal growth factor receptor like glycoprotein with tyrosine kinase activity.[9] Studies assessing links between prognosis and c-erbB-2 expression and squamous cell carcinoma in a variety of sites have yielded mixed results.[10-12] As of yet, however, there have been no studies evaluating the expression of the c-erbB-2 oncogene in one site in the head and neck, with long-term follow-up, utilizing whole organ sections. The purpose of this report was to study sections of whole organ specimens of supraglottic squamous cell carcinoma and assess for any links between c-erbB-2 expression and actual clinical outcome, as well as correlation with known clinicopathologic predictors of outcome.

MATERIALS AND METHODS

Patients and Tumor Specimens. Thirty-two supraglottic laryngeal squamous cell carcinomas were available from the Tucker Collection at the Albert Einstein Medical Center in Philadelphia, from patients treated at the Chevalier Jackson Clinic between 1962 and 1967. All patients underwent total laryngectomy, and 11 patients underwent primary neck dissection. There were no local recurrences. The age, sex, T stage of the primary lesion, lymph node involvement, histologic differentiation, distant metastatic disease, and patient survival in years were established from the patient records. There were 28 men and 4 women. The age distribution ranged from 36 to 72 years. The average length of follow-up was 5 years. The specimens consisted of whole organ sections that had been formalin-fixed, embedded in nitrocellulose, and sectioned at 10 µm. Approximately 40 sections per specimen were obtained and stained by hematoxylin and eosin (H & E; see Figure).

Immunohistochemistry. Immunohistochemistry

From the Department of Otorhinolaryngology–Head and Neck Surgery (Weinstein), the University of Pennsylvania Cancer Center (Nuamah), and the Department of Pathology and Laboratory Medicine (Montone), The University of Pennsylvania Medical Center, and the Division of Otolaryngology, The Albert Einstein Medical Center (Tucker), Philadelphia, Pennsylvania.

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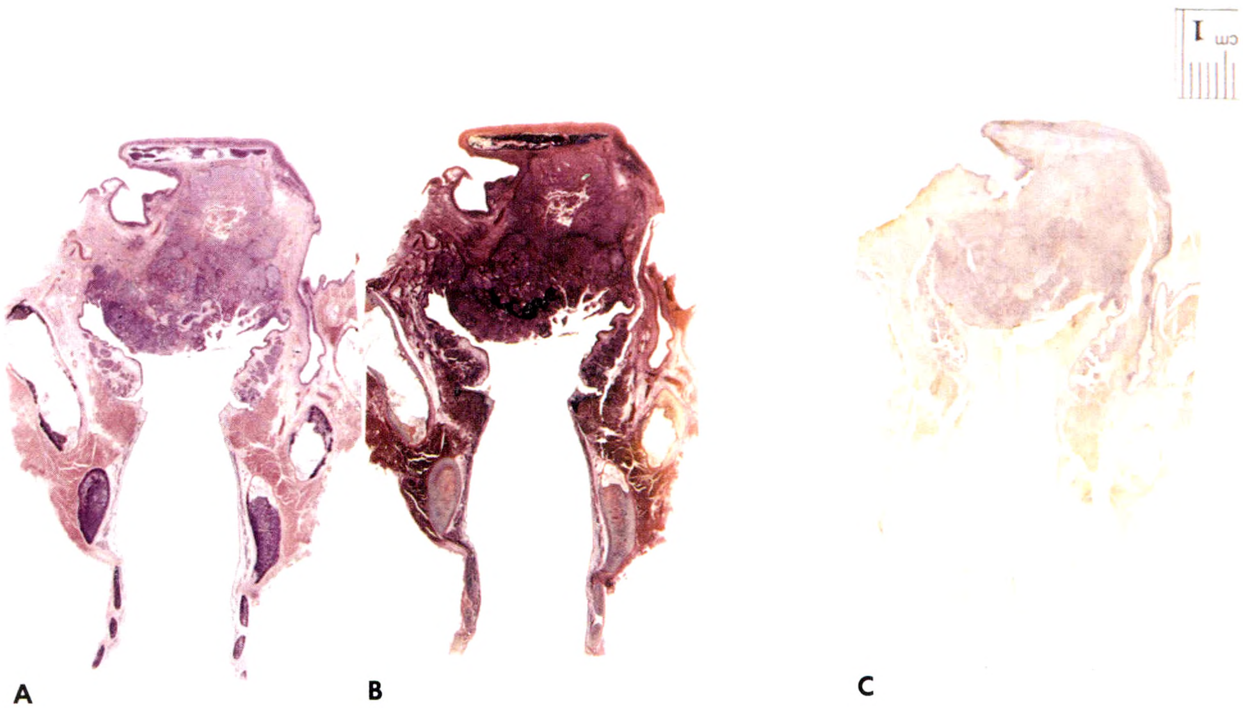

(Case 10) Whole organ section specimens stained with A) H and E, B) vimentin stain, and C) immune staining for c-erbB-2.

was employed using modifications of previous methods on destained H & E–stained sections using a polyclonal antibody targeting the cytoplasmic domain of the membrane-bound c-erbB-2 oncoprotein (Dako Corporation, Carpinteria, Calif). Briefly, the coverslips were removed by submerging the slides in xylene for 2 weeks. The de-coverslipped tissue sections were destained with 1% acid alcohol (Auto-Alcohol, Research Genetics, Huntsville, Ala), 50% alcohol and rehydrated with 1× universal buffer (Research Genetics). The c-erbB-2 primary antibody was diluted to 1:100 in Primary Antibody Diluent (Research Genetics) and incubated with tissue for 60 minutes at 45°C. The tissue sections were then washed with 1× Immuno/DNA buffer (Research Genetics) and incubated with a universal biotinylated secondary antibody system (Research Genetics) for 30 minutes at 45°C. The biotinylated primary-secondary antibody complexes were detected with streptavidin conjugated to horseradish peroxidase (Research Genetics) for 15 minutes at 45°C. Signal generation was performed with stable diaminobenzidine (Research Genetics) solution for 15 minutes at room temperature. The tissue sections were counterstained with hematoxylin and coverslipped with universal mount. All sections were evaluated by light microscopy. Positivity was scored according to the presence of membrane staining, in a blinded fashion by a board-certified pathologist (K.M.).

Negative controls included omission of the antibody from the assay. As a test for antigenicity of the specimens, an immunohistochemical staining for the neural marker S-100 was performed on one destained slide. Appropriate staining of nerves was seen.

Statistics. Two-tailed p values were obtained by using the Fisher's exact test as a test of independence, and the Cochran-Armitage test as a test of trend, where applicable. Odds ratios and the corresponding 95% confidence intervals were reported when the test of independence was significant. All p values were exact and computed with Statxact (Cytel Software Corporation, Cambridge, Mass).

RESULTS

A summary of the c-erbB-2 proto-oncogene detection in tumors of 32 patients with squamous cell carcinoma of the supraglottis with their clinicopathologic variables is presented in Table 1. Eleven of the 32 (34%) had evidence of c-erbB-2 positivity. All of the positive tumors showed heterogeneity in membrane immunostaining within the malignant portion of the sections, and no membrane immunostaining within the normal portions of the whole organ sections.

Evaluation of potential relationships between c-erbB-2 positivity and clinical parameters is shown in

TABLE 1. SUMMARY OF RESULTS OF c-erbB-2 DETECTION WITH POLYCLONAL ANTIBODY AND CLINICOPATHOLOGIC PARAMETERS IN 32 PATIENTS WITH SUPRAGLOTTIC CARCINOMA

*Case**	*Age*	*Sex*	*c-erbB-2 Protein*	*T Stage*	*Differentiation on Histology*	*Nodal Status*	*Metastasis*	*Death by Cancer*
17	62	M		4	Moderate			
73	69	M		4	Moderate	+		+
71	61	M		3	Well			
26	62	M		3	Well	+	+	+
105	36	M		3	Moderate			
60	53	M		2	Moderate			
83	66	M		2	Moderate	+		
37	65	M		3	Moderate			
49	62	M		2	Moderate			
61	66	M		3	Poor			
85	56	M		4	Moderate	+		
27	61	M		3	Well			
13	63	M		3	Moderate			
3	60	M		3	Moderate			
10	63	F		3	Well			
29	46	M		3	Well			
98	60	M		3	Poor	+		
81	55	M		2	Well	+		
9	53	M		2	Well			
41	69	M		3	Moderate			
30	51	M		3	Moderate			
34	66	M	+	3	Well	+	+	+
74	41	M	+	3	Moderate			
22	64	M	+	3	Moderate	+		
96	69	M	+	2	Moderate	+	+	+
65	48	F	+	2	Moderate	+		
111	57	F	+	2	Well			
79	58	M	+	2	Well			
11	72	M	+	3	Moderate	+	+	+
90	55	M	+	3	Moderate			
39	51	F	+	4	Moderate			
78	46	M	+	3	Well			

*Case number corresponds to case number in Tucker Whole Organ Section Collection, Albert Einstein Medical Center, Philadelphia, Pa.

Table 2. The parameters evaluated were T stage, histologic differentiation, nodal status, distant metastasis, and death by cancer. Statistical significance was not attained for any of the parameters evaluated when using the Fisher's exact test as a test of independence and the Cochran-Armitage test as a test of trend, where indicated.

A univariate analysis was done to assess for the effect of clinicopathologic parameters on metastasis. The parameters included T stage, histologic differentiation, presence of c-erbB-2 immunostaining, and joint presence of c-erbB-2 immunostaining and positive nodal status. The only parameter that indicated an effect on metastasis was joint presentation of c-erbB-2 immunostaining with positive nodal status. The odds ratio was 39.0 (2.41, 63.7), $p = .00760$. Positive nodal status without immunostaining of c-erbB-2 did not have a significant effect on metastasis.

DISCUSSION

The results in this study indicate that c-erbB-2 protein was immunohistochemically detectable in 34% of these selected squamous cell carcinomas of the supraglottic larynx. The use of whole organ specimens was useful in the detection of weak positivity in some cases, given the heterogeneity of the staining patterns, which was noted in all specimens. These findings are in accordance with other studies documenting an association between the observation of immunostaining of c-erbB-2 and squamous cell carcinoma of the head and neck.[13,14] Amplification of the c-erbB-2 gene has also been noted in squamous cell carcinomas of the head and neck, suggesting a role during cancer progression in culture.[15]

TABLE 2. ASSOCIATION BETWEEN CLINICOPATHOLOGIC PARAMETERS AND C-ERBB-2 EXPRESSION IN SQUAMOUS CELL CARCINOMA OF SUPRAGLOTTIC LARYNX

	c-erbB-2 Positive		*c-erbB-2 Negative*		
	No.	*%*	*No.*	*%*	*p*
T stage					
2	4	36	5	24	.8688
3	6	55	13	62	
4	1	9	3	14	
Differentiation					
Well	4	36	7	33	.8612
Moderate	7	64	12	57	
Poor	0	0	2	10	
Nodal status					
Positive	5	45	6	29	.4424
Negative	6	55	15	71	
Distant metastases					
Positive	3	27	1	5	.1055
Negative	8	73	20	95	
Death from cancer					
Positive	3	27	2	10	.3098
Negative	8	73	19	90	

Analysis of the prognostic value of immunodetection of c-erbB-2 in squamous cell carcinoma of the head and neck has been limited. One study that found no correlation between the presence of immune staining for c-erbB-2 and a variety of clinicopathologic prognostic factors was limited by analyzing a wide variety of primary sites.[13] Hou et al,[16] in a study limited to one site, oral squamous cell carcinoma, indicated that immunohistochemical detection of c-erbB-2 increased proportionally with increasing malignant phenotype. We noted that even though none of the tests correlating known clinicopathologic parameters in supraglottic squamous cell carcinoma with c-erbB-2 expression (Table 2) turned out to be statistically significant at the 5% level, whenever the c-erbB-2 oncogene was present the percentage of patients with nodal disease, distant metastases, and death by cancer was higher. This would suggest a poor prognosis in the presence of oncogene, but our small sample size resulted in our tests' not having enough statistical power to detect potential differences; a study of a larger series may be warranted.

Recent experimental and clinical evidence has linked the presence of c-erbB-2 with an increased rate of distant metastasis. Yu et al[17] utilized an experimental metastasis assay in nude Sprague-Dawley mice to show that human lung cancer cells transfected with human c-erbB-2 complementary DNA had enhanced metastatic potential due to promotion of invasion, as well as other steps in the metastatic cascade. Another study,[18] utilizing immuno–electron microscopy, noted that c-erbB-2 oncogene product stained positively on the microvilli of malignant cells with high growth potential, while those with low growth potential were devoid of staining. This study concluded that an increased number of microvilli correlated with an increased metastatic potential.[18] A clinicopathologic study of c-erbB-2 in patients with node-positive breast carcinoma revealed diminished survival when compared to patients who did not overexpress c-erbB-2.[19] Similarly, our study revealed that joint presentation of immune staining for c-erbB-2 and positive lymph node status was significantly associated with distant metastasis ($p = .00760$). All of the patients with distant metastasis in our series died of their disease (Table 1).

SUMMARY

Immune staining of supraglottic squamous cell carcinomas in whole organ sections with a polyclonal antibody for c-erbB-2 was noted in 34% of cases.

The use of whole organ specimens[20] was useful because of the heterogeneity of the staining pattern found in these specimens. Conversely, it is possible that immune staining for c-erbB-2 of small biopsy specimens may yield false negatives. We therefore recommend large samples for immune staining, preferably allowing for a cross section of the large portion of the lesion.

Although no statistically significant correlation was noted between the presence of immune staining for c-erbB-2 and clinicopathologic prognostic indicators, this may have been the result of sample size. The trend of higher percentages of patients with nodal disease, distant metastasis, and death by cancer in the presence of immune staining for c-erbB-2 warrants future studies on larger populations.

The highly statistically significant correlation between joint presentation of immune staining for c-erbB-2 and positive node status with distant metastasis may indicate that c-erbB-2 plays a role in the metastatic cascade in squamous cell carcinoma of the supraglottic larynx. Future studies are warranted.

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PEDIATRIC OTORHINOLARYNGOLOGY ENDOSCOPY DAYS

The First International Days in Pediatric Otorhinolaryngology Endoscopy will be held in Lyon, France, October 14-15, 1996. For further information, contact Marie-Claude Duchez, Departement d'ORL et de Chirurgie Cervico-Faciale, Hôpital E. Herriot, Place d'Arsonval, 69003 Lyon, France; fax 33 72 11 05 34.

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QUANTITATIVE VIDEOSTROBOSCOPIC MEASUREMENT OF GLOTTAL GAP AND VOCAL FUNCTION: AN ANALYSIS OF THYROPLASTY TYPE I

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The goal of surgical medialization of the vocal fold is to attain complete glottic closure. The purpose of this study is to quantify the glottal gap and to examine the relationship between glottal gap and vocal function perioperatively in thyroplasty type I. Glottal gap area was measured in 20 patients at the point of maximum closure of vocal fold vibration in digitized laryngeal stroboscopic images and was normalized by the square of vocal fold length. Glottal gap area thus measured was correlated with results obtained from well-accepted acoustic, aerodynamic, and perceptual measures of vocal function. The glottal gap was significantly reduced after thyroplasty type I. In patients with small preoperative glottal gaps, the amplitude of vocal fold vibration was significantly improved. This study verifies that quantitative videostroboscopic measurement of the glottal gap is a useful means of objective evaluation of glottic incompetence and of the results of thyroplasty type I.

KEY WORDS — glottal gap, quantitative measurement, thyroplasty type I, videostroboscopy, vocal function.

INTRODUCTION

There are well-accepted objective acoustic and aerodynamic measurements for evaluating changes in glottic efficiency and vocal function with thyroplasty type I.[1-12] Videostroboscopy has been the standard means of providing subjective perioperative evaluation of vocal fold vibration.[13] With the further development of videostroboscopic techniques, objective parameters based on video analyses have been introduced.[14] The purpose of this study is to quantify the glottal gap, and to examine the relationship between the glottal gap and vocal function perioperatively in patients undergoing thyroplasty type I. Digitized laryngostroboscopic images were analyzed for the quantitative measurements of glottal gap area and amplitude of vibration.

SUBJECTS

Thyroplasty type I was performed in 60 patients at Lenox Hill Hospital from 1987 to 1994. All patients who underwent vocal fold surgery before thyroplasty type I were excluded. Only patients who had previously undergone rigid telescopic laryngostroboscopy preoperatively and postoperatively with good visualization of the anterior commissure and the tip of the vocal process were selected for inclusion in the study. All patients who only had flexible fiberoptic endoscopy were excluded because of optical distortion with this technique. Twenty patients satisfied these criteria. Eighteen patients had unilateral vocal fold paralysis and 2 had vocal fold atrophy. Ages ranged from 25 to 83 years. The group demographics are shown in Table 1.

TABLE 1. SUBJECTS

Case	*Sex*	*Age*	*Diagnosis*	*Cause*
1	M	45	VFP, R	Idiopathic
2	M	64	VFP, R	Esophageal surgery
3	F	29	VFP, R	Neural tumor
4	F	43	VFP, R	Thyroid surgery
5	F	44	VFP, R	Thyroid surgery
6	F	50	VFP, R	Neural tumor
7	F	58	VFP, R	Laminectomy
8	F	59	VFP, R	Thyroid surgery
9	F	66	VFP, R	Lung surgery
10	F	74	VFP, R	Idiopathic
11	M	66	VFP, L	Cardiac surgery
12	M	69	VFP, L	Idiopathic
13	M	83	VFP, L	Cardiac surgery
14	F	15	VFP, L	Idiopathic
15	F	41	VFP, L	Thyroid surgery
16	F	45	VFP, L	Neural tumor
17	F	54	VFP, L	Traumatic
18	F	74	VFP, L	Vascular surgery
19	M	83	VFA, Bil	Idiopathic
20	F	25	VFA, L	Idiopathic

VFP — vocal fold paralysis, VFA — vocal fold atrophy, Bil — bilateral.

From the Ames Vocal Dynamics Laboratory, Lenox Hill Hospital, New York, New York.

Presented at the meeting of the American Laryngological Association, Palm Desert, California, April 29-30, 1995. Dr Omori received the Young Faculty Honorable Mention Award for 1995 from the Association.

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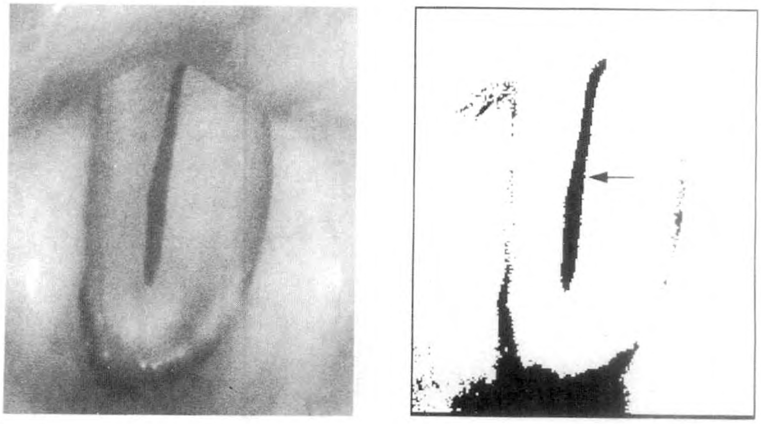

Fig 1. (Case 10) Measurement of glottal gap area (arrow). At left is digitized image, and at right, traced image.

METHODS

Direct laryngostroboscopy and vocal function studies including acoustic, aerodynamic, and perceptual analyses were undertaken preoperatively and postoperatively in the Ames Vocal Dynamics Laboratory, Lenox Hill Hospital.

The patients were asked to phonate a sustained vowel /i/ at their habitual pitch and loudness. Vocal fold vibration during phonation was simultaneously monitored and recorded through a 70° telescope (Nagashima Co, Tokyo, Japan) connected to a charge-coupled device video camera (Toshiba Corp, Tokyo). A 60-mm zoom lens was used to magnify and focus the image of the vocal fold. Illumination was provided by a stroboscopic xenon light source (Nagashima Co, Tokyo). Laryngostroboscopic images were recorded with a CVD-1000 Hi8 computer video deck (Sony Corp, Tokyo) at 30 frames per second. Recorded sequential images of vocal fold vibration were played back frame by frame on the video deck with Momento software (Kohshin Graphic Systems Inc, Tokyo). Only video frames that satisfied the strict selection criteria were identified for digitization. With a Color Space II videographics card (MASS Microsystems Inc, Sunnyvale, Calif), images were digitized and stored in a Macintosh IIcx computer (Apple Computer Inc, Cupertino, Calif). Thereafter, laryngeal images were retrieved by Image software (National Institutes of Health, Bethesda, Md) and displayed on a monitor. Glottal gap area was then measured by the difference between the color density of the vocal fold and the glottal gap semiautomatically (Fig 1). After the threshold of color density was set at the appropriate level, the traced glottal gap was calculated and expressed in square pixels. Membranous vocal fold length was measured from the point of the anterior commissure to the point of the tip of the vocal process and expressed in linear pixels (Fig 2). Membranous vocal fold length on the unaffected side was chosen in the patients with vocal fold paralysis. In patients with vocal fold atrophy, membranous vocal fold length on the nonoperative side was measured. In the digitized images, the glottal gap area was measured at the maximum closed point of vibration and was normalized by the square of the membranous vocal fold length, hereinafter termed the normalized glottal gap area. Normalized glottal gap area (units) = glottal gap area (pixels × pixels)/(membranous vocal fold length)^2 (pixels × pixels) × 100.

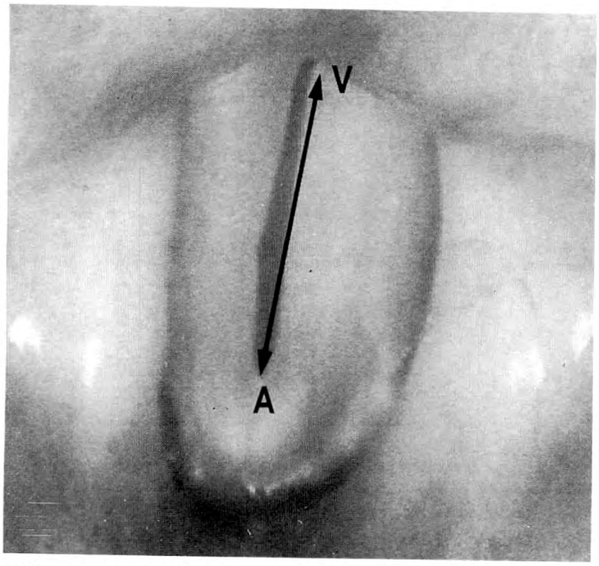

Fig 2. (Case 10) Measurement of membranous vocal fold length. A — anterior commissure, V — tip of vocal process.

The amplitude of vocal fold vibration was measured by determining the difference between the vocal fold widths at the maximum closed and the maximum opened points of vibration. The vocal fold width was measured at the middle portion of the vocal folds and expressed in linear pixels (Fig 3). Amplitude was normalized by membranous vocal fold length, hereinafter termed normalized amplitude. Normalized amplitude (units) = amplitude (pixels)/membranous vocal fold length (pixels) × 100.

In acoustic analysis, pitch perturbation, amplitude perturbation, signal to noise ratio, harmonics to noise

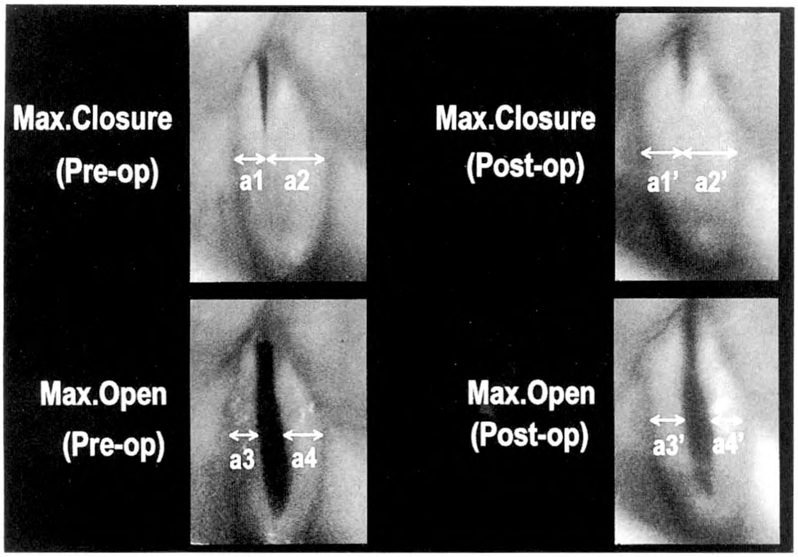

Fig 3. (Case 6) Measurement of amplitude of vocal fold vibration. For preoperative amplitude, right vocal fold is a1 minus a3, and left vocal fold is a2 minus a4. For postoperative amplitude, right vocal fold is a1' minus a3', and left vocal fold is a2' minus a4'.

ratio, breathiness index, high-frequency power ratio, and turbulent noise ratio were examined for a sustained vowel sound /a/ in comfortable phonation.[3-9] H index was examined in the consonant-vowel combination /hai/.[10] A B & K 4006 condenser microphone and a Sony PCM-2500A digital audiotape recorder were used for data acquisition. Sound collection was performed in a sound-treated booth. The distance from the microphone was set at 20 cm. The data, stored on a digital audiotape, were then transferred to a Macintosh IIx computer (Apple Computer Inc) through a direct digital interface (Digidesign Inc, Menlo Park, Calif). All the analyses were performed with a software (C language) program written by members of the Ames Vocal Dynamics Laboratory.[8-10]

Aerodynamic analysis included mean flow rate, AC/DC ratio, and maximum phonation time measured for a sustained vowel sound /u/ in comfortable phonation.[11] Measurement of airflow was made by a PA 500 Phonation Analyzer high-frequency response hot-wire flowmeter (Minato Co, Tokyo). A software program written in C language was used to acquire, store, and analyze the data from the PA 500.[12]

In perceptual evaluations, the voice data of sustained vowel sound /a/ were played back through a 16-bit digital-to-analog converter and Bose speakers. Degree of breathiness was scored as 0, 1, 2, or 3 by three experienced otolaryngologists. Score 3 was given for severely breathy voices and score 0 was given for normal voices. The scores were averaged and classified again into four categories: score 0, 1, 2, or 3.[15]

All the statistical analyses in this study were performed with SPSS software (SPSS Inc, Chicago, Ill).

RESULTS

Figure 4A shows the preoperative and postoperative normalized glottal gap areas in the 20 patients. The preoperative normalized glottal gap area ranged from 0.7 to 15.2 units (mean 6.3 units, SD 4.8 units). The postoperative normalized glottal gap area ranged from 0 to 6.7 units (mean 1.5 units, SD 1.7 units). The normalized glottal gap area was significantly reduced by thyroplasty type I ($p < .01$, Wilcoxon test). In the 8 patients with a preoperative normalized glottal gap area of less than 4 units, there was little improvement in glottal gap area. However, in these 8 small-gap patients, normalized amplitude was significantly increased postoperatively ($p < .01$, Wilcoxon test), as shown in Table 2.

Relationships between the normalized glottal gap area and the acoustic, aerodynamic, and perceptual parameters were examined in the 20 patients. All the acoustic parameters (pitch perturbation, amplitude perturbation, signal to noise ratio, harmonics to noise ratio, breathiness index, H index, high-frequency power ratio, and turbulent noise ratio) had significant correlations with the normalized glottal gap area (Pearson's correlation coefficients). Of these acoustic parameters, harmonics to noise ratio correlated best with the normalized glottal gap area (Fig 4B). All the aerodynamic parameters (mean flow rate, AC/DC ratio, and maximum phonation time) also had significant correlations with the normalized glottal gap area (Pearson's correlation coefficients). Of these aerodynamic parameters, mean flow rate correlated most strongly with the normalized glottal gap area (Fig 4C). Coefficients of correlation with the normalized glottal gap area are shown in Table 3. By analysis of variance, the normalized glottal gap area showed significant differences in four categories of percep-

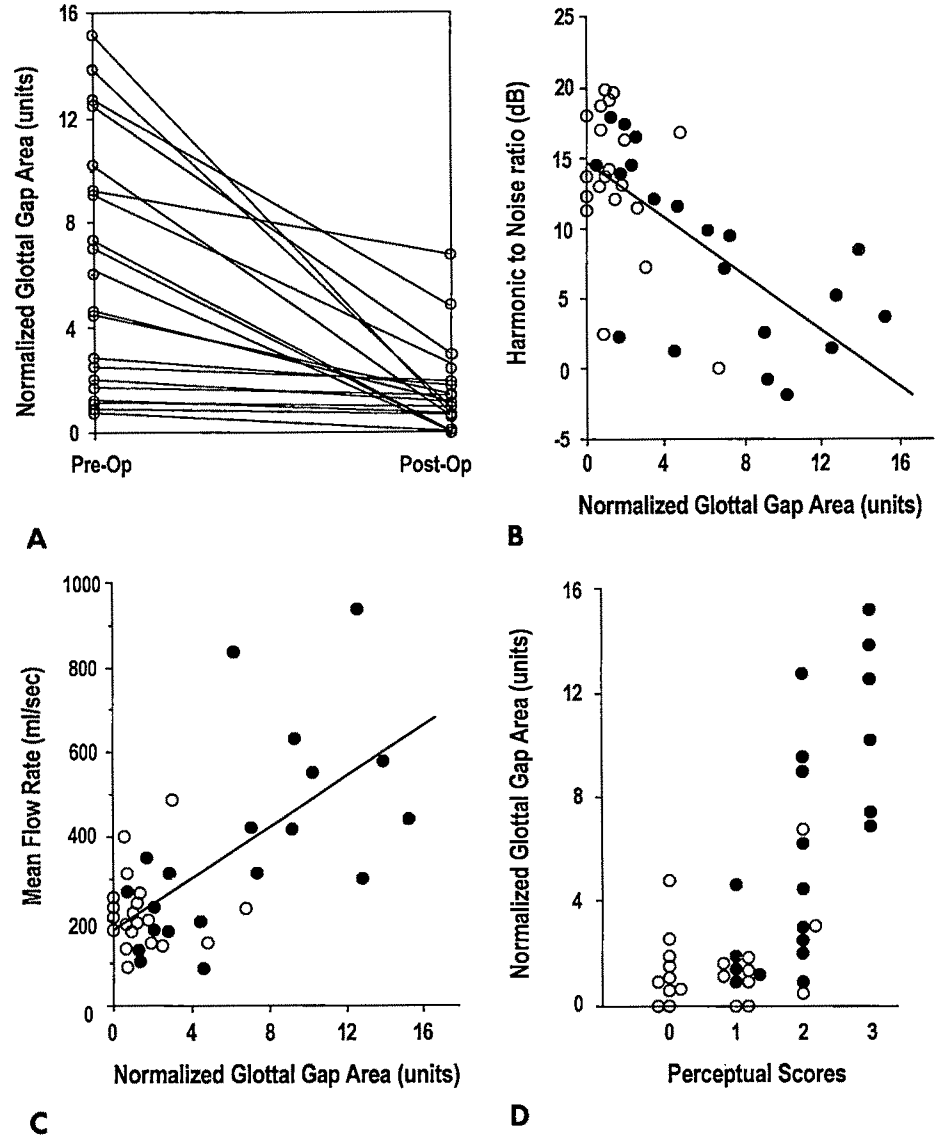

Fig 4. Results. A) Perioperative changes of normalized glottal gap area. B-D) Filled circles — preoperative values, empty circles — postoperative values. B) Relationship between normalized glottal gap area and harmonics to noise ratio. C) Relationship between normalized glottal gap area and mean flow rate. D) Normalized glottal gap area for each perceptual score of breathiness.

tual scores ($p < .01$; Fig 4D).

DISCUSSION

Clinical application of videostroboscopy is limited by the lack of objective measures of vocal fold vibration. This paper presents a method of obtaining objective measurements of vocal fold vibration by utilizing digitized laryngostroboscopic images. The glottal gap area is measured dynamically at the point of maximum closure. This technique also provides a quick calculation of amplitude for each vocal fold. Of equal importance is the fact that the measurements can be made by means of a stroboscope and a personal computer with proprietary hardware and software. In contrast, high-speed motion picture photography is cumbersome, expensive, time-consuming, and not clinically applicable in its current configuration.[16] Sercarz et al[14] reported an office-based system for quantitative measurement of laryngeal videostroboscopic images and presented a few cases utilizing stroboscopic image analysis for the measurement of glottal gap area and symmetry of vocal fold excursion. High-speed video systems have been described for the measurement of glottic area in several reports; however, image quality and system costs remain problems.[17,18]

Laryngostroboscopic images were analyzed subjectively by Bless et al.[13] Their visual-perceptual classifications, however, do not provide quantitative assessment of vocal fold vibration. In our current study, outcome analysis of thyroplasty type I is performed by means of objective measurements with videostroboscopy. With the measurement of the normalized glottal gap area, it is possible to quantitatively document the amount of glottal gap reduction by thyroplasty type I expressed in numeric units. In addition to glottal gap area, the status of mucosal vibration, especially amplitude, is an important de-

TABLE 2. NORMALIZED AMPLITUDE IN PATIENTS WITH SMALL PREOPERATIVE GLOTTAL GAPS

		Normalized Amplitude (units)	
Case	*Side*	*Preop*	*Postop*
3	R	6.7	9.9
	L	3.8	6.1
6	R	1.3	3.7
	L	6.1	7.8
8	R	4.8	10.6
	L	4.0	5.9
14	R	3.9	8.0
	L	7.7	8.1
15	R	3.9	4.0
	L	0.4	4.8
16	R	5.2	5.4
	L	20.4	10.8
19	R	3.7	7.4
	L	2.2	3.8
20	R	4.3	7.2
	L	4.0	4.1

TABLE 3. CORRELATIONS BETWEEN NORMALIZED GLOTTAL GAP AREA AND ACCEPTED PARAMETERS

Parameter	*Correlation Coefficient*
Pitch perturbation	.615*
Amplitude perturbation	.540*
Signal to noise ratio	−.494*
Harmonics to noise ratio	−.654*
Breathiness index	.627*
H index	−.435*
High-frequency power ratio	.573*
Turbulent noise ratio	.643*
Mean flow rate	.644*
AC/DC ratio	−.458*
Maximum phonation time	−.423*

*$p < .01$.

terminant of vocal function. In the 8 patients who had a small glottal gap area preoperatively, there was a slight improvement of glottal gap area plus a significant increase in the amplitude of vocal fold vibration postoperatively. We may conclude that thyroplasty type I improves the amplitude of vocal fold vibration and the glottal gap. The increased amplitude of vibration and improved glottic competence lead to increased loudness.

In this study, we excluded all patients who only had flexible fiberoptic endoscopy because of optical distortion with this technique. Yanagisawa and Yanagisawa[19] have demonstrated that a telescopic view had no distortion when the telescope was positioned in the midline of the tongue and oropharynx. Objective video analysis can only be performed accurately when the image displays the anterior commissure and the tip of the vocal process simultaneously. We also excluded all patients who had prior vocal fold surgery. These restrictions limited the number of patients included in this study to 20 patients out of 60 patients undergoing thyroplasty type I, excluding numerous cases with excellent results.[2,20]

The technique of videostroboscopic image analysis is limited by the nature of both stroboscopy and telescopy. Stroboscopy is not suited to the assessment of patients with severe aperiodic vibration of the vocal fold. Because telescopy does not provide a three-dimensional image of the larynx, our glottic measurements are two-dimensional and do not account for glottic incompetence due to malalignment in the glottic plane.

In the present study, relative units of glottal gap area and amplitude are used because exact measurement cannot be determined. The glottal gap area and amplitude in the digitized images are dependent on the distance from a telescope. Although pixels are objective values, they require calibration based on distance between a telescope and the vocal folds. Therefore, mathematic transformations were used to determine normalized measurements.

The membranous vocal fold length was utilized for normalization to control changes in image size due to the vertical motion of the telescope. The amplitude of vocal fold lateral excursion is a linear parameter and was normalized with a one-dimensional value of membranous vocal fold length (pixels). The glottal gap area is a two-dimensional measure and was therefore normalized by the square of the membranous vocal fold length (pixels × pixels). The normalization is limited by the nature of the vocal fold length, because the vocal fold length during phonation is affected by variables such as pitch, loudness, and the compensatory activity of extrinsic muscles. In our study, videostroboscopic image analysis provides glottic measurements at the patient's habitual pitch and loudness. Vocal fold length on the unaffected side was chosen for normalization in our study because of the shortening of the paralyzed vocal fold.[21]

Our current study has shown that a reduced glottal gap area correlates with an improvement of vocal function as determined by acoustic, aerodynamic, and perceptual measures. All the acoustic parameters (pitch perturbation, amplitude perturbation, signal to noise ratio, harmonics to noise ratio, breathiness index, H index, high-frequency power ratio, and turbulent noise ratio) had significant correlations with the glottal gap area. Of these parameters, the harmonics to noise ratio correlated most strongly with the glottal gap area. The harmonics to noise ratio may be the most sensitive acoustic parameter, because it includes pitch perturbation, amplitude perturbation, and turbulent noise. The aerodynamic parameters (mean flow rate, AC/DC ratio, and maximum phonation time) had significant correlations with the glottal gap area. Of these three, mean flow rate is the most sensitive, perhaps because the AC/DC ratio is influenced by the efficiency of vocal fold vibration, and the maximum phonation time is influenced by the vital capacity of the lung. Although these parameters give us an objective standard of voice quality and vocal efficiency, they do not allow an assessment of vibration of each individual vocal fold. Videostroboscopic image analysis provides a direct measurement of glottic incompetence and demonstrates the effect of surgical medialization. This technique is applicable to any form of medialization procedure, including arytenoid adduction, injections, and reinnervation.

The glottal gap is a component of many varieties of dysphonia. The normalized glottal gap area offers an accurate means of objectively measuring the glottal gap area. Quantitative measurement of glottic images can therefore be utilized in a variety of clinical settings.

CONCLUSIONS

1. Videostroboscopic image analysis provides clinically applicable objective measurements of vocal fold vibration.

2. The normalized glottal gap area correlates with accepted acoustic, aerodynamic, and perceptual measurements.

3. Videostroboscopic image analysis allows objective assessment of the vibration of each vocal fold individually.

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BILATERAL EVOKED OTOACOUSTIC EMISSIONS IN A CHILD WITH BILATERAL PROFOUND HEARING LOSS

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Recording of bilateral evoked otoacoustic emissions in a 3-year-old girl with bilateral profound hearing loss is presented. No component of auditory-evoked brain stem potentials was recorded. Findings on computed tomography of the inner ear were within normal limits. At retest 3 months later, these results were unchanged. Explanations for this particular condition are presented together with a review of the literature.

KEY WORDS — child, evoked otoacoustic emissions, profound hearing loss.

INTRODUCTION

In 1948 Gold[1] predicted the existence of evoked otoacoustic emissions (EOEs) in the external ear canal. However, it was not until 1978 that such emissions were recorded by Kemp,[2] who demonstrated that acoustic emissions could be found in the human outer ear canal in response to acoustic clicks or to short tone bursts. Several arguments suggest that the outer hair cells of the organ of Corti are related to EOE production; however, the mechanism of EOEs is still under debate.[3]

Numerous authors reported that the recording of EOEs in infants in whom hearing loss was suspected allowed us to assume that the peripheral hearing ability was sufficient for the maturation of hearing pathways and for the development of speech.[4,5] Therefore, this test has been widely advocated as a screening procedure for auditory dysfunction in children and infants.

In this report we document a case of bilateral EOEs recorded in a child with bilateral profound hearing loss. A review of the three cases previously reported in the literature is performed to allow for interpretation of this particular condition and discussion of the future management in terms of speech and language rehabilitation.

CASE REPORT

A 3-year-old girl with a delay in speech was brought to our department by her mother. Pregnancy and delivery were unremarkable, as was the family past medical history. Otolaryngological and pediatric examinations yielded normal findings. Initial free field audiometric results are presented in Fig 1. Tympanograms were normal. The contralateral stapedius reflex was absent in both ears. A laboratory and serologic workup failed to provide any etiologic information.

Evoked otoacoustic emissions were recorded with the ILO88 Otodynamics system (nonlinear click stimulation, click 80 microseconds, analysis time 20 milliseconds, 260 stimuli) in a soundproof room. A normal response was recorded in both ears (Fig 2).

Findings of auditory brain stem evoked response (ABR) testing (monaural stimulation via earphones with contralateral masking, stimulus click 0.150 milliseconds, signal filtered between 160 Hz and 3,400 Hz, responses averaged 1,600 times) performed under sedation are presented in Fig 3. At stimulation at 100 dB hearing level (HL) on right and left ears, no response was achieved.

At retest 3 months later these results were unchanged. Computed tomography of the petrous bone, internal ear canal, and cerebellopontine angle showed

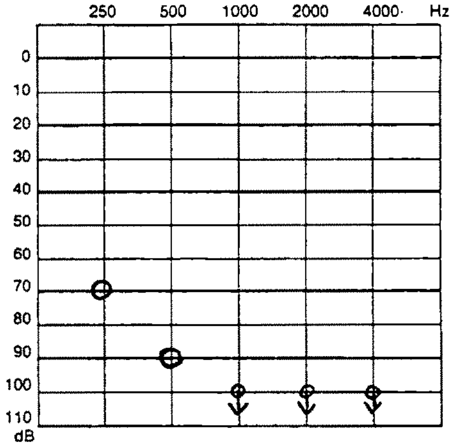

Fig 1. Pure tone audiogram: free field analysis.

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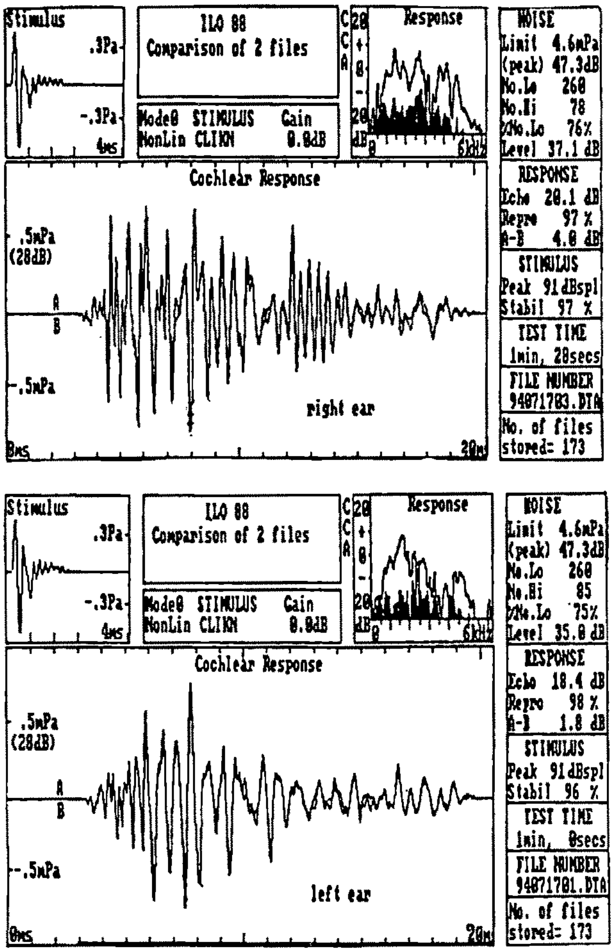

Fig 2. Click-evoked otoacoustic emissions.

no abnormality. The parents refused the completion of cochlear electrostimulation and electrocochleography and chose the sign language method for this young girl, who is now 4 years old.

DISCUSSION

The detrimental effects of severe and profound deafness on the development of appropriate speech, language, and cognitive abilities in infants is a well-recognized notion.[5-9] The early detection and management of this handicap is one of the keys to successful rehabilitation.[6,8-10]

In 1982 the American Joint Committee on Infant Hearing issued a position recommending that rehabilitation should begin by the age of 6 months once the handicap is diagnosed.[6]

The common techniques available for evaluating hearing function in infants include behavioral audiometry and ABR. At the present time, ABR is believed to provide the most accurate information on hearing levels for the 2- to 4-kHz frequencies in infants.[7,10] It is objective and noninvasive and is not affected by drugs or sleep. However, completion of this test is time-consuming. Recently, EOEs have been reported to be an objective, noninvasive, and easy test for auditory function.[7,11,12]

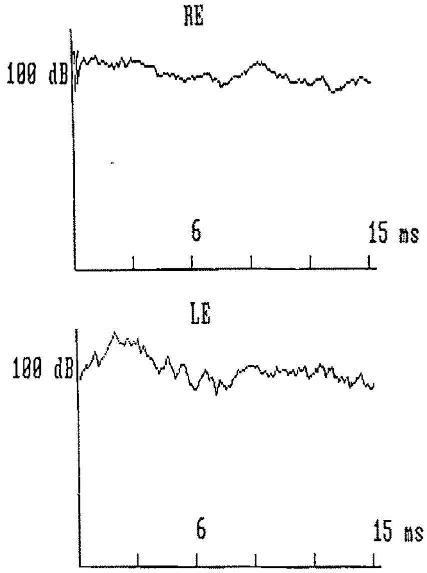

Fig 3. Auditory brain stem evoked responses. RE — right ear, LE — left ear.

In 1988, Bonfils et al[7] reported that the presence of EOEs was correlated with the ABR wave V threshold. In this study, based on the analysis of 46 ears, EOEs were never recorded in infants with ABR thresholds higher than 40 dB HL. Therefore, Bonfils et al considered that EOEs could be considered, in infants and neonates, as a screening test with a screening level at 30 dB HL. According to Zwicker and Schorn[5] and Schorn,[10] the recording of EOEs excludes with a "very high probability" a peripheral hearing loss that might influence the development of speech. Our case, as well as the three cases[13-15] previously reported in the English-language medical literature, demonstrates that the recording of EOEs in patients with severe or profound sensorineural hearing loss is a rare but not impossible event. Such a condition might be due to retrocochlear disease, neural damage, or inner hair cell damage. In all three cases in the literature,[13-15] as well as in our case, normal computed tomography findings in the cerebellopontine angle ruled out a space-occupying tumor. The completion of electrocochleography or electrostimulation of the cochlear nerve allows us to distinguish cochlear dysfunction from neural damage. In the case reported by Lutman et al,[13] electrocochleography noted measurable compound action potentials documenting a good cochlear function and therefore indicating neural damage. In the case described by Welzl-Müller et al,[15] the successful stimulation of the cochlear nerve ruled out neural damage and therefore suggested that the inner hair cells were damaged. Electrocochleography and electrostimulation of the cochlear nerve were not performed in the case reported by Prieve et al,[14] or in our case (parents' refusal). It is therefore not possible in these two cases to specify whether inner hair cells and/or nerve fibers were damaged. The distinction between inner hair cell damage and neural damage appears to be a key point for the choice of the rehabilitation method in patients with bilateral profound hearing loss presenting EOEs. Hearing aids cannot be considered, and some functional nerve fibers must be present to consider cochlear implantation. Management of the child in our case was not considered, as the parents preferred sign language and refused any form of surgery as soon as the diagnosis of bilateral profound hearing loss was made.

Our report, as well as the review of the literature, demonstrates that EOEs might be recorded in patients with severe or profound deafness. The use of EOEs in screening for hearing disorders in newborns and infants should not be questioned, as the condition reported in the present study is an extremely rare event.

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LARYNGEAL PLEOMORPHIC RHABDOMYOSARCOMA

A CRITICAL REVIEW OF THE LITERATURE

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A case report of pleomorphic rhabdomyosarcoma of the larynx is presented. It is the first case in which the diagnosis is supported by immunohistochemical investigation. A critical review of the literature follows, evaluating the clinicopathologic features of this rare malignancy.

KEY WORDS — immunohistochemistry, larynx, pleomorphic rhabdomyosarcoma.

INTRODUCTION

Malignant mesenchymal tumors of the larynx are extremely rare.[1] With the adoption of immunohistochemical staining techniques, it is now apparent that most cases of alleged malignant soft tissue neoplasms of the larynx were, in fact, spindle cell squamous carcinoma. Rhabdomyosarcomas are soft tissue sarcomas and represent 40% of sarcomas occurring in the head and neck. The larynx is rarely involved, and this location represents only 3% of all rhabdomyosarcomas of the head and neck. The literature contains some unconvincing reports, but several well-documented and acceptable cases of laryngeal rhabdomyosarcoma have been reported. All histologic variants of rhabdomyosarcoma have been described in the larynx.[2] This paper describes a case of pleomorphic rhabdomyosarcoma of the larynx, the first to be presented in the literature with the support of immunohistochemical investigations.

CASE REPORT

A 69-year-old man was referred to the Department of Otolaryngology of Treviso Hospital with a progressively worsening dysphonia that had lasted 7 months. He was a smoker (15 cigarettes a day), was a nondrinker, and had no relevant clinical history. It was impossible to perform indirect laryngoscopy because of pharyngeal hyperreflexia. On palpation, no lymph nodes were detectable in the neck. Direct microlaryngoscopy showed a smooth mass arising from the right true vocal cord, which released a gelatinous material on incision. The histologic diagnosis of the biopsy specimens from the tumor was leiomyosarcoma. The microscopic slides were reexamined at Padua University, and the lesion was consequently diagnosed as pleomorphic rhabdomyosarcoma. A neck computed tomography (CT) scan confirmed the clinical examination and demonstrated a large mass arising from the right true vocal cord and protruding into the airway without regional metastases. A systemic metastatic workup (including chest radiography, bronchoscopy, and lung-mediastinum-abdomen CT scan) was negative. After consultation with medical oncologists and radiotherapists, total laryngectomy was performed, associated with total

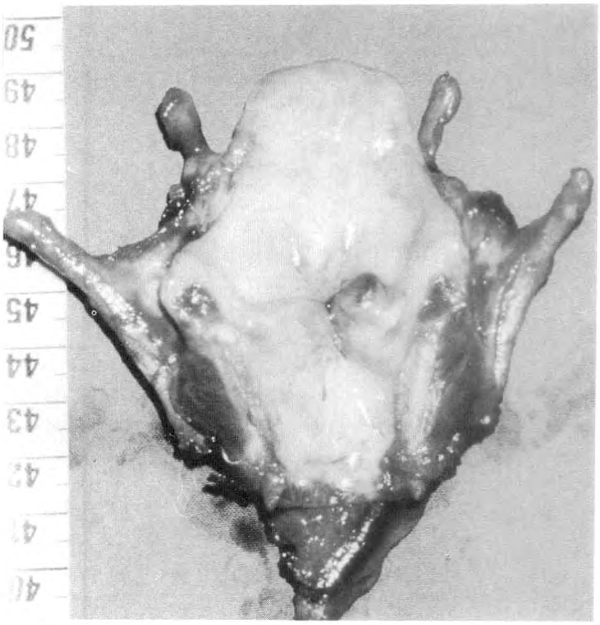

Fig 1. Operative specimen showing tumor involving right true vocal cord extending in subglottic region.

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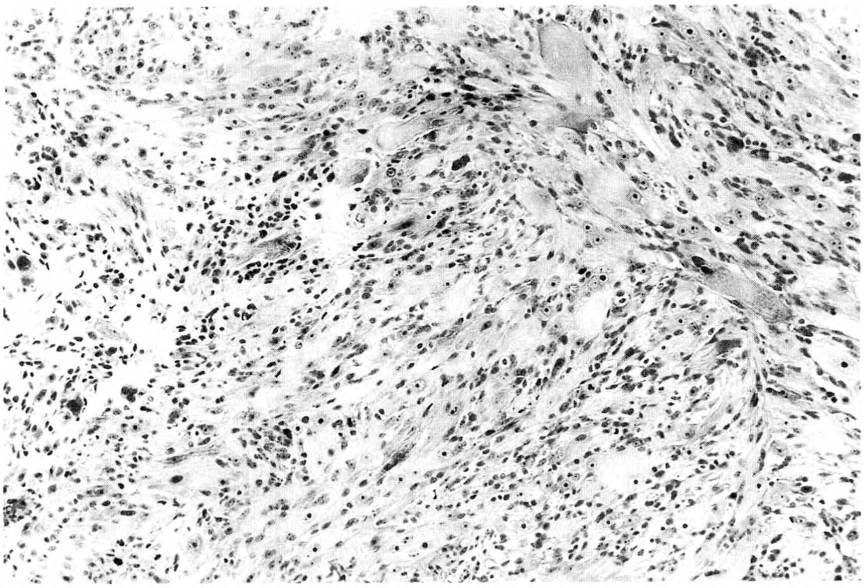

Fig 2. Histologic pattern of lesion showing great variety of cells (H & E, original ×40).

thyroidectomy because of a woody thyroid gland found at surgery. The laryngeal tumor in the right true vocal cord measured 20 × 25 mm. The surgical specimen was sent for histologic examination, and on the basis of the light microscopic and immunohistochemical findings, the diagnosis of pleomorphic rhabdomyosarcoma of the larynx and chronic Riedel's thyroiditis was reached. External radiotherapy was administered (6,000 cGy over 6 weeks in 30 fractions). The patient tolerated the therapy well, with no major side effects, and was further seen at regular intervals. At the last checkup, 2 years after surgical treatment, he had neither signs of local recurrence nor clinically detectable metastases.

METHODS

The resection specimen was fixed overnight in 10% neutral-buffered formalin, and routine histologic sections were taken from the lesion and stained with hematoxylin and eosin. Immunohistochemical analysis was performed on paraffin sections with the avidin-biotin-peroxidase complex immunoperoxidase technique. The sections were stained with use of the following antibodies: vimentin (V9), desmin (D33), muscle-specific actin (HHF35), myoglobin (MG1), fast skeletal muscle myosin (MY32), S-100 protein (polyclonal antiserum), and cytokeratin (Cam 5.2).

PATHOLOGY

The specimen consisted of the resected larynx (Fig 1). The lesion was of lobulated appearance and firm consistency; it involved the right true vocal cord and extended into the subglottic region. Microscopically (Figs 2-5), the tumor was composed of large pleomorphic spindle-shaped or strap-like cells with abundant deeply eosinophilic, granular, or finely vacuolated

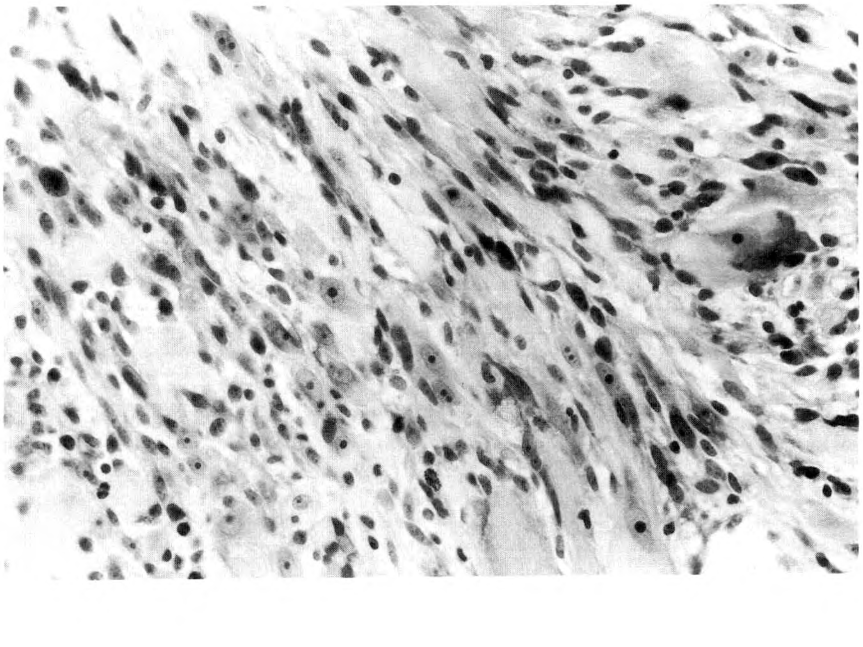

Fig 3. Area of tumor composed predominantly of spindle cells (H & E, original ×100).

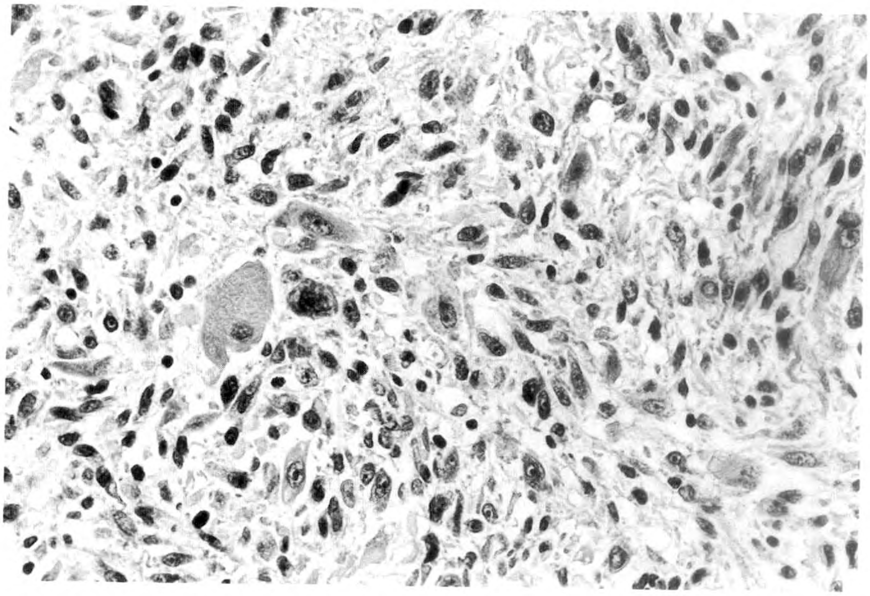

Fig 4. Pleomorphic appearance of tumor showing many cells varying in size and shape (H & E, original ×100).

cytoplasm. These elements were often gigantic and monstrous in aspect and were associated with lymphohistiocytic infiltrate. Often, two or more nuclei were located peripherally. Nucleoli were also present. Mitoses were abundant. No cross-striations were identified in the sections stained with hematoxylin and eosin. Skeletal muscle differentiation was confirmed in the neoplastic elements by immunoreactivity for fast skeletal muscle myosin and muscle-specific actin. Myoglobin was detected in well-differentiated rhabdomyoblasts. Desmin was observed in cells of muscle differentiation. Vimentin was present in many tumor cells. There was no staining for antibodies to cytokeratin or S-100 protein.

DISCUSSION

Rhabdomyosarcoma is defined as a malignant tumor whose only identifiable line of differentiation is that of a rhabdomyoblast.[3] Other tumors may contain rhabdomyoblast differentiation, even in the larynx.[4,5] Rhabdomyosarcoma is a histologically diverse malignant soft tissue neoplasm and is rarely diagnosed in the larynx. The classification of rhabdomyosarcomas remains somewhat controversial, although the most commonly accepted system includes three major types: the embryonal and its botryoid variant, the alveolar, and the pleomorphic. Rhabdomyosarcomas of the larynx are usually seen in children, and the histologic morphology is usually of the embryonal type. Laryngeal pleomorphic rhabdomyosarcomas are very rare, and in a number of reported cases the pathologic details are incomplete or without illustrations,[6] or it proved impossible to establish the correlation between morphologic and clinical findings.[7] The case reported by Kleinsasser and Glanz[8] has not been included, because it was

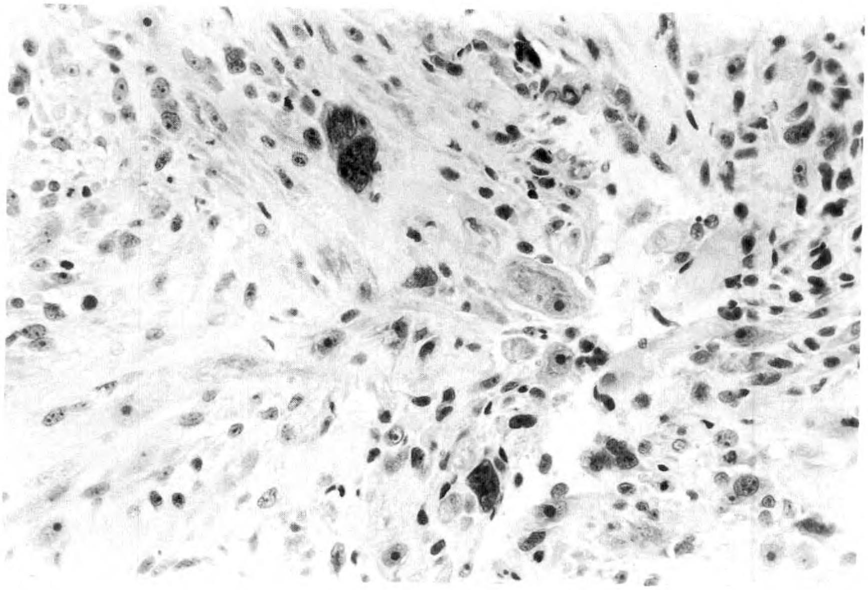

Fig 5. Another area of lesion showing giant cells with centrally located large nuclei, evident nucleoli, and abundant eosinophilic, granular cytoplasm (H & E, original ×100).

TABLE 1. REPORTED CASES OF PLEOMORPHIC RHABDOMYOSARCOMA OF LARYNX

Authors	*Year*	*Age (y)*	*Sex*	*Site*	*Management*	*Follow-up*
Filipo and Crifò[11]	1964	53	M	Left false vocal cord, ventricle	Total laryngectomy, radiotherapy	NED at 8 mo
Rodriguez and Ziskind[12]	1970	57	M	Anterior two thirds of right true vocal cord, anterior commissure	Total laryngectomy	No follow-up
Grouls and Bechtelsheimer[13]	1974	67	M	Left vocal cord	Radiotherapy	Died after 3 wk (cardiogenic shock)
Frugoni and Ferlito[14]	1976	33	M	Left true and false vocal cords	Partial laryngectomy, radiotherapy	NED at 6 y
Lamendola and Buonocore[15]	1977	61	M	Middle third of upper surface of right true vocal cord	Total laryngectomy, bilateral neck dissection	NED at 1 y
Marasso et al[16]	1977	65	M	Right false vocal cord, extending into subglottis	Radiotherapy, chemotherapy	No follow-up
Winther and Lorentzen[17]	1978	72	M	Left vocal cord	Partial laryngectomy	No follow-up
Franz[18]	1979	57	M	Left vocal cord	Radiotherapy	NED at 2 y
De Agostino et al[19]	1988	70	M	Middle third of left vocal cord, anterior commissure	Total laryngectomy	No follow-up
Jahnke and Vogl[20]	1994	45	M	Right vocal cord	Total pharyngolaryngectomy, cervical esophageal and tracheal resection, right hemithyroidectomy, chemotherapy, radiotherapy	No follow-up
Present case	1996	69	M	Right true vocal cord, extending into subglottis	Total laryngectomy, thyroidectomy, radiotherapy	NED at 2 y

NED — no evidence of disease.

considered by the authors as a mixed type. The case described by Dodd-O et al[9] as pleomorphic rhabdomyosarcoma occurring in a 5-year-old boy was probably a case of embryonal botryoid rhabdomyosarcoma. In one instance, the publication could not be obtained and had to be excluded.[10] Excluding the above cases, therefore, there appear to be 10 fully documented and acceptable cases in the literature (Table 1[11-20]), and our report is the first case in which the histologic diagnosis is supported by immunohistochemical study (Table 2).

TABLE 2. IMMUNOHISTOCHEMICAL FINDINGS

Antiserum	*Clone or Code No.*	*Source*	*Dilution*	*Immuno-staining*
Vimentin	V9	Dako	1:20	Positive
Desmin	D33	Dako	1:200	Positive
Muscle-specific actin	HHF35	Dako	1:100	Positive
Myoglobin	MG1	Dako	1:4	Positive
Fast skeletal muscle myosin	MY32	Immunon	1:10	Positive
S-100 protein	poli	Dako	1:5,000	Negative
Cytokeratin	Cam 5.2	Becton Dickinson	1:20	Negative

Laryngeal pleomorphic rhabdomyosarcomas have been observed in patients from 33 to 72 years of age (mean, 59 years), and all the patients were men. The tumor has occurred mainly in the glottic area (9/11 cases), and in 2 cases the glottic mass extended into the subglottis. The symptom at presentation was usually dysphonia. In 1 case, acute respiratory distress and weight loss were also reported, while another 2 patients suffered from cough.

The treatment varied. Total laryngectomy was performed in 6 cases; in 3 of these, it was followed by radiotherapy, with associated chemotherapy in 1. In 1 patient the laryngeal treatment was accompanied by bilateral neck dissection, while in another a pharyngectomy with cervical esophageal and tracheal resection was done. A partial laryngectomy was used in 2 patients and only 1 of these was irradiated. Two patients were treated with radiotherapy alone; in 1 case, this was associated with chemotherapy. Follow-up is only available for 6 cases and ranges from 8 months to 6 years. One patient died of cardiogenic shock after 3 weeks.

The identification of this neoplasm may be difficult, particularly when the diagnosis has to be made on biopsy material. The morphologic diagnosis is based primarily on conventional light microscopy and is confirmed by immunohistochemical and ultrastructural investigations.

The main differential diagnosis involves leiomyosarcoma, malignant fibrous histiocytoma, and malignant mesenchymoma. The initial biopsy-based diagnosis in our case was leiomyosarcoma. Immunohistochemistry is an essential tool for differential diagnosis. Immunohistochemical stains for desmin, myoglobin, and muscle-specific actin are usually positive. The tumor may also express positivity for vimentin. Desmin is not specific for skeletal muscle and is also seen in some leiomyosarcomas, but the latter is less often positive. Myoglobin is specific only for skeletal muscle, and leiomyosarcoma is consequently negative for it, and also for fast skeletal muscle myosin. Conversely, rhabdomyosarcoma is negative for smooth muscle–specific actin; leiomyosarcoma is positive. Malignant fibrous histiocytoma may be positive for α-1-antichymotrypsin and α-1-antitrypsin, and even focally positive for desmin, and it is myoglobin-negative. Malignant mesenchymoma is extremely rare in the larynx,[21] and this neoplasm shows at least one other distinctive sarcomatous pattern, such as osteosarcoma, chondrosarcoma, or liposarcoma, in addition to the rhabdomyosarcomatous component.[22]

Surgery is the treatment of choice for pleomorphic rhabdomyosarcoma of the larynx. Conservative laryngeal surgery should be employed if the tumor can be adequately removed, and it has proved successful in the past. Large tumors may require total laryngectomy. Considering the absence of metastases to cervical lymph nodes in all cases reported in the literature (apart from 1 case[20] in which two positive lymph nodes were removed together with the primary lesion), elective neck dissection is not recommended, since this would represent overtreatment. Distant metastases have not been reported in this form of laryngeal rhabdomyosarcoma. The role of chemotherapy in the management of this subtype is still undefined. Recent reports employing triple therapy (ie, surgery, irradiation, and chemotherapy) have been most encouraging in the embryonal and botryoid types of laryngeal rhabdomyosarcomas. Both have a tendency to metastasize to regional lymph nodes and lung. The exact role of radiotherapy continues to be debated. There are only 2 instances in which it was used alone: in 1 case the patient was alive after 2 years, while the other died of cardiogenic shock after 3 weeks.

We think it is important to separate the adult or pleomorphic rhabdomyosarcoma of the larynx from the other subtypes, because its different biologic behavior implies differences in its treatment and prognosis.

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ATLANTO-AXIAL SUBLUXATION AND CERVICAL OSTEOMYELITIS: TWO UNUSUAL COMPLICATIONS OF ADENOIDECTOMY

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Grisel's syndrome (atlanto-axial subluxation) and cervical osteomyelitis are two unusual complications of adenoidectomy. We present two patients; one with atlanto-axial subluxation following uncomplicated tonsillectomy and adenoidectomy, and one with cervical osteomyelitis following uncomplicated adenoidectomy. Both patients presented with persistent postoperative neck pain. Surgical intervention, as well as long-term intravenous antibiotics, was required. A high index of suspicion, as well as cervical spinal series with flexion-extension views, is necessary for diagnosis. Flexible nasopharyngoscopy and computed tomography of the cervical spine also aided in diagnosis and treatment planning. With early diagnosis and proper treatment, the prognosis is good. Neurologic sequelae were prevented in both of our patients.

KEY WORDS — adenoidectomy, atlanto-axial joint subluxation, cervical osteomyelitis, complications, Grisel's syndrome.

INTRODUCTION

Adenoidectomy with or without tonsillectomy is one of the most common surgical procedures, being performed over 300,000 times per year.[1] Neck pain occurs in up to 10% of patients after adenoidectomy.[2] This is frequently attributed to reflex irritation of the cervical muscles due to inflammation from adjacent tissue spaces[3]; however, more serious causes, including infection and cervical spinal subluxation, should be considered in the differential diagnosis. Atlanto-axial subluxation (Grisel's syndrome) is a rare complication that has been well described in the literature.[4-7] Cervical osteomyelitis is an extremely unusual and, to our knowledge, previously unreported infectious complication of adenoidectomy. The following is a discussion of two cases: one of cervical osteomyelitis following uncomplicated adenoidectomy, and the other of atlanto-axial subluxation following uncomplicated tonsillectomy and adenoidectomy (T & A). We will review the literature and discuss the appropriate workup and treatment of these rare complications.

CASE REPORTS

Case 1. A previously healthy 11-year-old girl underwent a T & A for recurrent tonsillitis and adenotonsillar hypertrophy. There was no history of trauma prior to surgery, and a preoperative soft tissue lateral radiograph of the neck was significant only for moderately enlarged adenoid tissue with no bony abnormalities (Fig 1A).

An uncomplicated T & A was performed in the Rose position with a suction electrocautery set on 40 (Valleylab 2). The adenoids were noted to be 90% obstructing the nasopharynx. The patient received preoperative intravenous (IV) penicillin G sodium and was discharged the same day on a 7-day course of oral penicillin V potassium.

Two weeks later, the patient presented to the clinic with complaints of persistent neck pain. She was afebrile, with normally healing tonsil fossae. The patient was unable to extend her neck without severe discomfort and had very limited side-to-side mobility. There was intense spasm of the sternocleidomastoid and paraspinous muscles. Posteroanterior and lateral cervical spine radiographs showed no evidence of soft tissue swelling or bony abnormalities. She was treated for skeletal muscle spasm and returned for follow-up 2 weeks later with improvement of her symptoms.

The patient presented 5 months later to the emergency department with persistent neck stiffness and pain. She remained afebrile, but flexible nasopharyngoscopy revealed granulation tissue in the nasopharynx, and there was persistent spasm of the paraspinous muscles. Neurologic examination showed no focal deficits. The white blood cell count was 7,700 with a normal differential, and the erythrocyte sedimentation rate was slightly elevated at 21 mm/h. A cervical spine series revealed subluxation of C-1 on C-2 with erosion of the odontoid process (Fig 1B,C). This was confirmed by computed tomography (CT; Fig 1D), which, in addition, demonstrated an atlanto-dental interval of 1.4 cm and prevertebral soft tissue swell-

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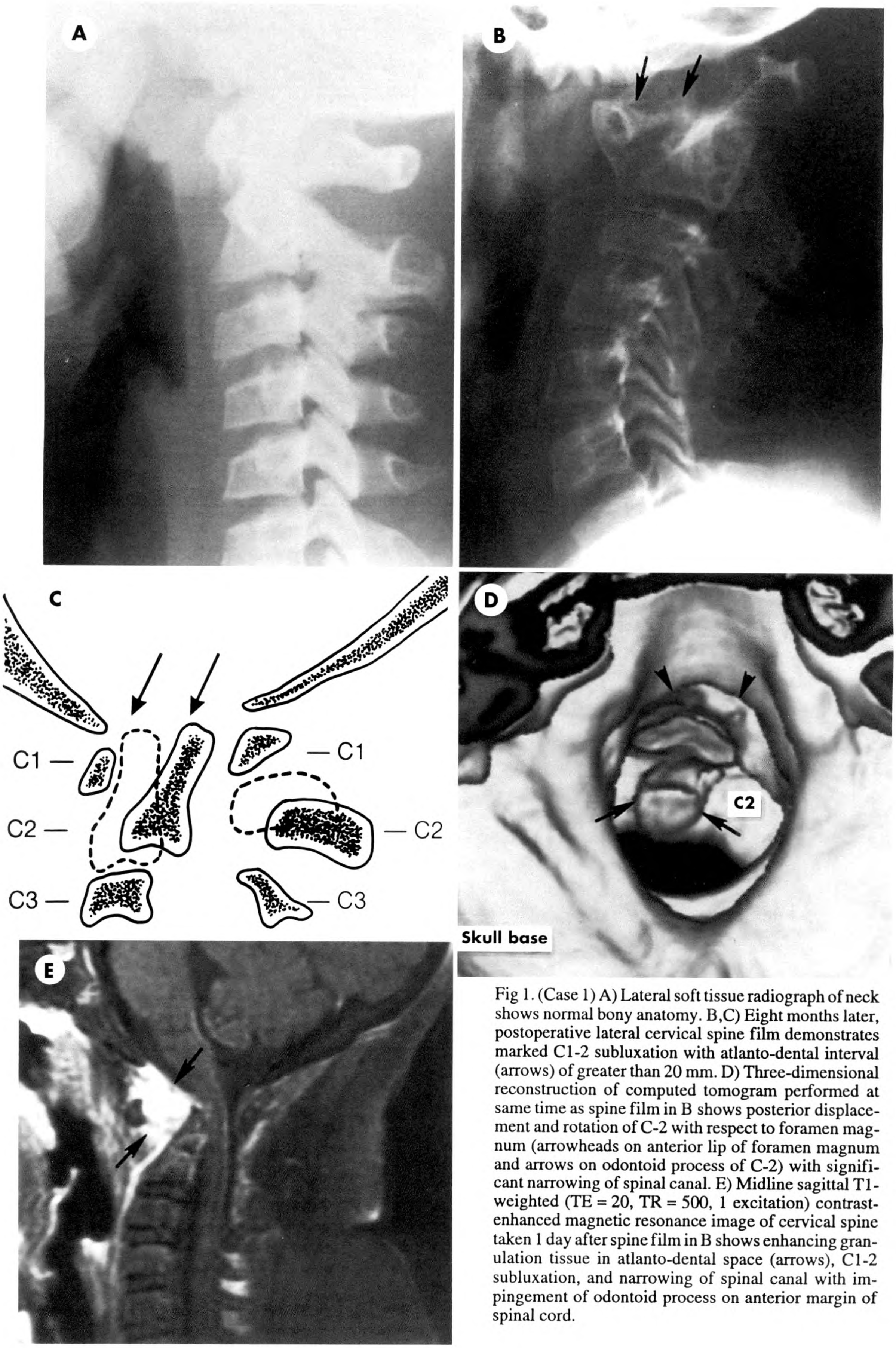

Fig 1. (Case 1) A) Lateral soft tissue radiograph of neck shows normal bony anatomy. B,C) Eight months later, postoperative lateral cervical spine film demonstrates marked C1-2 subluxation with atlanto-dental interval (arrows) of greater than 20 mm. D) Three-dimensional reconstruction of computed tomogram performed at same time as spine film in B shows posterior displacement and rotation of C-2 with respect to foramen magnum (arrowheads on anterior lip of foramen magnum and arrows on odontoid process of C-2) with significant narrowing of spinal canal. E) Midline sagittal T1-weighted (TE = 20, TR = 500, 1 excitation) contrast-enhanced magnetic resonance image of cervical spine taken 1 day after spine film in B shows enhancing granulation tissue in atlanto-dental space (arrows), C1-2 subluxation, and narrowing of spinal canal with impingement of odontoid process on anterior margin of spinal cord.

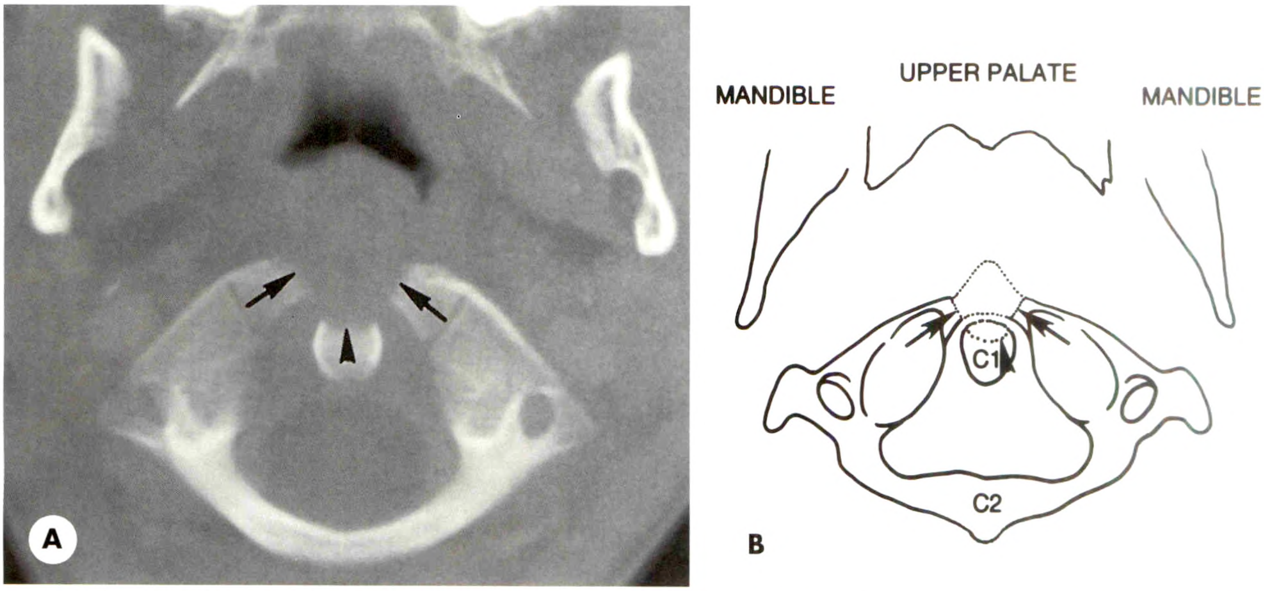

Fig 2. (Case 2) A) Postoperative axial computed tomogram of neck at level of C-1 ring shows prevertebral soft tissue mass with adjacent erosion of anterior arch of C-1 (arrows) and of anterior cortex of odontoid process of C-2 (arrowhead). B) Diagram of A.

ing that enhanced on magnetic resonance imaging with gadolinium (Fig 1E).

The patient was admitted to the neurosurgery service, started on IV clindamycin phosphate, and placed in Gardner-Wells tongs for progressive in-line traction for 10 days. At the end of this time, she underwent placement of a halo for stabilization. Serial cervical spine radiographs during this time showed gradual improvement of alignment. She received a 4-week course of IV clindamycin and upon completion remained unstable out of the halo. She therefore underwent posterior cervical stabilization.

Nine months later the patient is neurologically intact with resolution of her neck pain but some persistent decreased range of motion of her neck.

Case 2. A 5-year-old boy presented to the otolaryngology clinic for evaluation and treatment of conductive hearing loss, recurrent acute otitis media, snoring, and mouth breathing. He underwent an uncomplicated adenoidectomy with placement of bilateral pressure equalization tubes under general anesthesia. He was placed in the Rose position, and a suction electrocautery set on 40 was used for removal of the adenoid tissue, which was 80% obstructing the nasopharyngeal airway. Intravenous penicillin was given preoperatively, and the patient was discharged home the same day on a 7-day course of oral amoxicillin.

Six weeks postoperatively, the patient had persistent neck pain and a mass was noted in the nasopharynx. A CT scan, in addition to the mass, revealed bony erosion of the anterior arch of C-1 (Fig 2). Flexion-extension films of the cervical spine were negative for instability (subluxation). His white blood cell count was 8,400, with a normal differential, and his erythrocyte sedimentation rate was also normal.

A neurosurgery consultation was obtained; the patient was placed in a Philadelphia collar and started on IV clindamycin phosphate. Nasopharyngoscopy under general anesthesia showed granulation tissue and erosion of the posterior bony nasopharynx consistent with osteomyelitis (Fig 3). Histology confirmed the inflammatory nature of the mass, and culture and sensitivities showed normal throat flora.

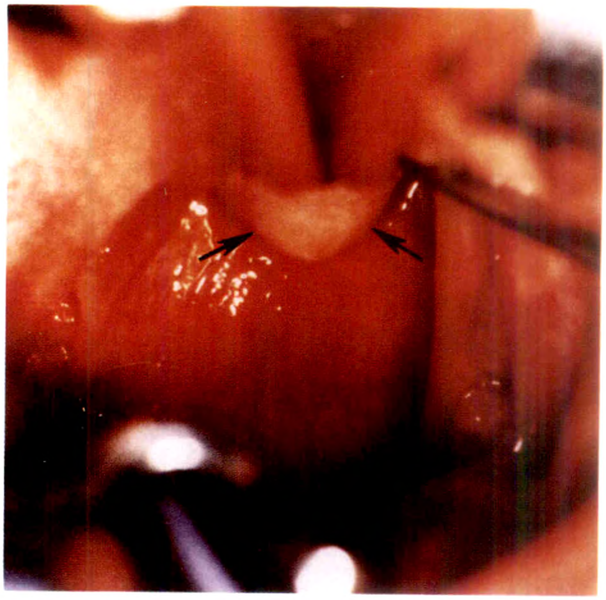

Fig 3. (Case 2) Intraoperative view of oropharynx with palate retracted showing granulation tissue on posterior nasopharyngeal wall (arrows).

Fungal and acid-fast cultures were negative. The patient received a 4-week course of IV clindamycin at home while stabilized in a Philadelphia collar. A follow-up flexion-extension film showed no instability. His neck pain and stiffness completely resolved.

DISCUSSION

Grisel's syndrome (atlanto-axial subluxation) is a spontaneous dislocation of C-1 on C-2 without known trauma or organic disease of the bone. It was first described by Bell[4] in 1830, but has come to be known as Grisel's syndrome after P. Grisel,[5] a French otolaryngologist who, in 1930, described the syndrome in two young girls following nasopharyngitis. Grisel's syndrome occurs most commonly in children 5 to 12 years of age, and there is no sex predominance.[6] It usually follows head and neck infections or otolaryngological procedures. It is a rare complication of T & A: of 62 reported cases of nontraumatic atlanto-axial subluxation reported between 1830 and 1985, 4 occurred after tonsillectomy and 2 after adenoidectomy.[7]

The mechanism for Grisel's syndrome is generally believed to be hyperemia following infection or surgical trauma that leads to decalcification of the anterior arch of the atlas and laxity of the anterior transverse ligament between the atlas and the axis.[8]

Parke et al[9] gave an anatomic rationale for this condition. They described a plexus of veins called the pharyngovertebral veins that drain the posterior-superior nasopharynx and lateral pharyngeal recesses and empty into the periodontoidal plexus and ultimately into the upper cervical spine.

An even rarer complication, cervical osteomyelitis, was reported by Tami et al[10] following an uncomplicated tonsillectomy in a 21-year-old man under general anesthesia. This patient did not progress to dislocation, however, and was successfully treated with a 6-week course of intravenous penicillin. The authors believe that the infection of the cervical spine was due to hematogenous seeding during transient bacteremia, as there was no clinical evidence of postoperative pharyngeal lymphadenitis or abscess.

Diagnosis and Treatment. Early diagnosis of cervical osteomyelitis and/or atlanto-axial subluxation is imperative to prevent neurologic sequelae and requires a high index of suspicion in patients with postoperative neck pain. Patients with atlanto-axial subluxation usually complain of stiff neck and present with spasm of either the sternocleidomastoid or deep cervical muscles. The patient will hold his or her head in a fixed position, which is typically tilted to one side with slight rotation toward the opposite side and slight flexion. This position has been likened to that of a robin listening for a worm, or the so-called cock-robin position.[11] Local tenderness can often be appreciated over the atlanto-axial joint posteriorly, and occasionally the spinous process of the axis is palpable away from the midline toward the affected side (Sudek's sign).[12] Radiographic evaluation should include posteroanterior and lateral cervical spine films with an open mouth view as well as lateral flexion-extension views. On the lateral view there may be an increase of the atlanto-dental interval, the space between the posterior margin of the anterior arch of the atlas and the odontoid process. In addition, demineralization of the odontoid may be seen.

We have found flexion-extension views to be very useful in picking up mild subluxation. Computed tomography (with or without three-dimensional imaging) is useful in defining bony destruction and malalignment.

The presentation of cervical osteomyelitis is very similar. These patients may also have decreased neck mobility and muscle spasm; however, the position of the neck will vary. Patients are more often toxic-appearing, with fever and a high white blood cell count[3]; the erythrocyte sedimentation rate may be elevated as well. Lateral radiographs of the neck will demonstrate a loss of normal prevertebral soft tissue planes over the affected disk space. Demineralization may not be apparent on plain films, and thus CT is often employed.[3] Magnetic resonance imaging can be useful to demonstrate enhancement of infected soft tissue, and bone scanning may be employed to confirm the diagnosis. Flexible nasopharyngoscopy is very helpful in visualizing granulation tissue in the nasopharynx.

The treatment of cervical osteomyelitis should include a long course (4 to 8 weeks) of intravenous antibiotic therapy coupled with cervical stabilization.[10] Patients should also be taken to the operating room for surgical debridement of infected areas and tissue culture.

If there is C1-2 subluxation, treatment is required to reduce the risk of permanent restriction of cervical motion or neurologic sequelae. Treatment should be individualized depending on the degree and duration of the subluxation.[11] In addition to antimicrobial therapy, the dislocation should be reduced. If the anterior transverse ligament is intact, cervical traction with a hard cervical collar for 6 to 8 weeks is usually sufficient. If the ligament is deficient, cervical skeletal traction with Gardner-Wells tongs implanted in the skull may be required to effect reduction. Immobilization of the cervical spine with a Minerva cast or halo vest is recommended to allow the ligaments to heal. If, following immobilization, there is an atlanto-dental interval of greater than 4.5 mm on lateral flexion cervical spine films, posterior fusion of C1-2 should be considered. If patients have subluxation longer than 3 months, Fielding and Hawkins[11] recommend primary C1-2 fusion to decrease the risk of neurologic sequelae.

In our experience, patients presenting with early neck pain following tonsillectomy and/or adenoidectomy should be treated with organism-specific antibiotics covering resistant strains for a minimum of 7 days in the hope of eradicating early nasopharyngitis and preventing its sequelae.

CONCLUSION

Cervical osteomyelitis is a serious, unusual complication of adenoidectomy, which, if undetected, can lead to instability of the cervical spine and serious neurologic sequelae. A high index of suspicion is required for diagnosis. Any persistent neck pain should be vigorously worked up to rule out an infectious complication. With proper diagnosis and treatment, serious sequelae can be avoided, and the prognosis is good.

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SPONTANEOUS OTOGENIC PNEUMOCEPHALUS

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A very rare case of otogenic pneumocephalus in a healthy 24-year-old man with a widely pneumatized right mastoid, precipitated by forceful Valsalva's maneuver, is reported. When a pneumocephalus is suspected, computed tomography scans are mandatory. The pertinent literature is discussed and the potential mechanisms causing spontaneous pneumocephalus are described. To the best of our knowledge, only two other similar cases have been reported up to now.

KEY WORDS — mastoid pneumatization, middle ear, pneumocephalus, Valsalva's maneuver.

INTRODUCTION

Spontaneous otogenic pneumocephalus is very rare.[1] Although pneumocephalus is quite common following trauma, especially with a fracture involving the paranasal sinuses, it is rare as a manifestation of chronic otitis media or as a complication of mastoid surgery.[1-4] Pneumocephalus has also been associated with carcinoma of the maxillary sinus,[5] epidermoid tumor of the ethmoid sinus,[6] cerebrospinal fluid shunts,[7] and functional endoscopic sinus surgery.[8] In addition, pneumocephalus has been reported as a complication of epidural anesthesia[9,10] and nasotracheal intubation.[11]

In 1989, Nolla-Salas et al[12] reported 13 cases of pneumocephalus: 7 caused by trauma, 5 following surgical procedures, and 1 caused by barotrauma. Andrews and Canalis[1] reviewed 54 cases of otogenic pneumocephalus and added 5 cases of their own. In their cases the most common etiologic factor was trauma (36%), followed by otitis media (30%) and otologic surgery (30%).

On reviewing the literature we found only two reports of pneumocephalus of spontaneous origin,[13,14] one of them[14] reporting a case of a large intracranial pneumatocele arising from mastoid air cells. The symptoms appeared after multiple coughing spells and the patient required a craniotomy for repair of the dural hiatus.

We thought it would be of interest to report a case of intracranial pneumocephalus caused by Valsalva's maneuver in a 24-year-old man with extensive pneumatization of the right mastoid.

CASE REPORT

A 24-year-old man was admitted to the neurosurgical department of the Freiburg University clinic. Three weeks before his admission he complained of bilateral scotoma and 1 week later he complained of headaches. The attending physician diagnosed a slight papilledema in both eyes. No other eye abnormalities were found. A computed tomography (CT) scan was performed and showed wide pneumatization of the right mastoid compared to the left mastoid, with a small defect of the right lamina interna (see Figure, A). A significant pneumocephalus at the height of the mastoid cells in the parietal area was also found, with slight displacement of brain tissue (see Figure, B). The patient was examined by the Department of Otorhinolaryngology, too, and we elicited from the anamnesis that the patient had for years had a habit of performing Valsalva's maneuver, which was diagnosed as a nervous tic.

The otolaryngological findings were normal, including those of pure tone audiometry, speech audiometry, tympanometry, and bilateral stapedius reflex testing. Laboratory test results were normal. The patient was operated on under general anesthesia and a right temporo-occipital osteoclastic craniotomy was performed. The right mastoid cells were found to be of free contour, and the dura was widely adherent to the bone and in some regions elevated from the bone by air, but intact, not infiltrated, and therefore not resected. A mastoidectomy was performed and the mastoid cells were thoroughly opened, the mucosa was removed, and the mastoid was obliterated by bone wax and collagen for prevention of a recurrence. The skull defect was closed by bone cement

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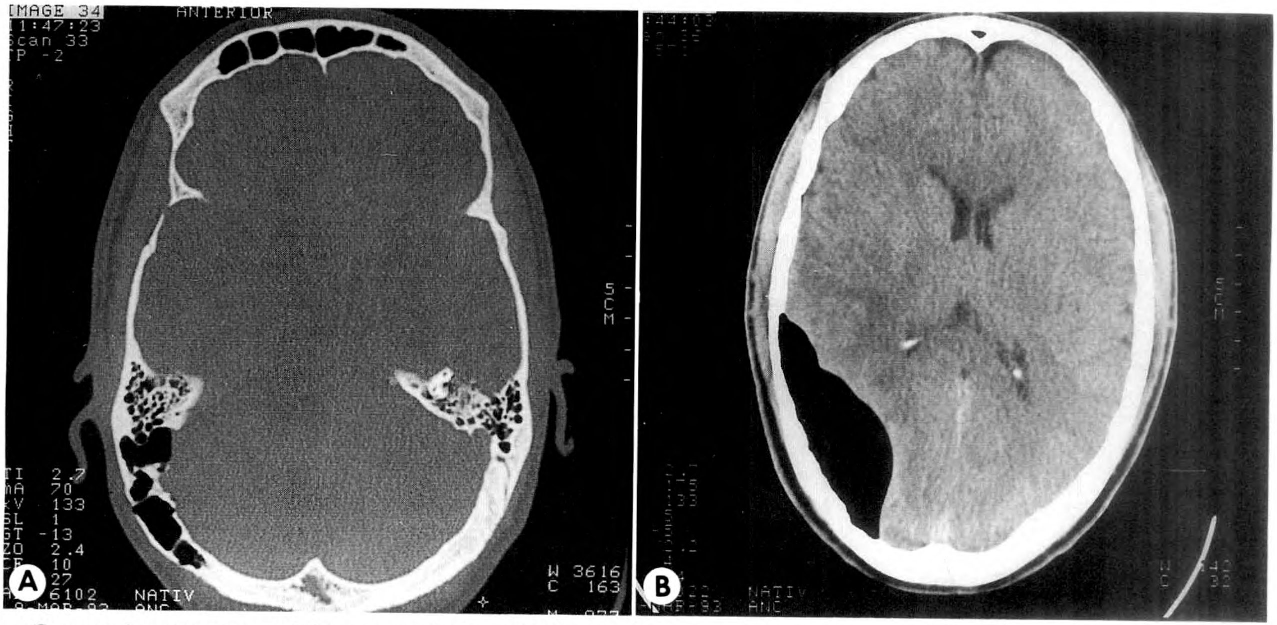

Computed tomograms. A) Wide pneumatization of right mastoid compared to left and small defect of tabula interna. B) Huge pneumocephalus of right temporo-parieto-occipital hemisphere. Displacement of brain tissue can be seen.

(Palacos). Several biopsy specimens were taken from the bone overlying the pneumocephalus and were found to involve a bone cyst without signs of inflammation, malignancy, or specificity. The postoperative course was uneventful. The patient was followed up for 1 1/2 years and no recurrence of the pneumocephalus was found.

DISCUSSION

Spontaneous otogenic pneumocephalus is extremely rare.[13,14] In 1965, Ahren and Thulin[15] described a case with lethal intracranial complications following paracentesis and inflation with a Politzer balloon in the external auditory canal. The inflation caused detachment of the dura mater over the tegmen tympani, with bleeding from a meningeal vessel causing instantaneous compression and damage to the brain. The precondition for such a detachment was the occurrence of a bony defect of the tegmen tympani. In a number of cadaver cases those authors found that bone defects in the tegmen tympani were comparatively common. The distribution of the pneumatic cells in the temporal bone has been thoroughly studied by Wolff et al[16] and Dietzel.[17] They found that the extent of pneumatization of the mastoid and petrous pyramid ranged from small cell groups around the mastoid antrum to extensive cell formations in squamous temporal bone, in the apex of the pyramid and the retrosinus area. Dietzel[17] also reported that over the last 80 years there has been a marked tendency for increase in pneumatization of the temporal bone.

In our case extensive pneumatization of the right temporal bone with a thin septum and a small defect in the tabula interna of the skull overlying the dura were found. In order for an otogenic pneumocephalus to occur, there must be a break in the cranial cavity that allows air to enter. This means communication between the middle ear and the middle or posterior fossa.[1] It is also necessary that middle ear pressure increase over the intracranial pressure in order to permit air to enter the cranium.

One mechanism by which a pneumocephalus occurs is the presence of a continuous cerebrospinal fluid leak that results in the development of a relatively negative intracranial pressure, allowing lost fluid to be replaced by air.[18]

Another mechanism was reported by Horowitz[19] and called the "ball valve effect." The process may be envisaged as follows. First, there is a break in the bone overlying the dura. Second, the air enters the middle ear through the eustachian tube as nasopharyngeal pressure rises during forced swallowing, the act of coughing or sneezing, or forced Valsalva's maneuver. Third, the air becomes trapped between the bone and the overlying dura by the ball valve mechanism, which allows air to enter but not to leave the defect.[1,19] This results in an epidural pneumocephalus, as in our case. If there is also a dura defect, the air may enter the subdural space, causing a subdural pneumocephalus.

Epidural pneumocephalus is the rarest form, as the dura is highly adherent to the calvarium. The epidural pneumocephalus appears as an air pocket that is not dependent on head position.[20] Subdural air collections, which are dependent on head position, are seen more frequently.[1,20]

The clinical symptoms of otogenic pneumocephalus are often vague,[1,9,10,13,14] presenting a challenge for the otologist. When the origin is traumatic, the CT scan is usually diagnostic. When the cause is otitis media, a CT scan is not always performed, and then the diagnosis is delayed.[1] In our case the presenting symptom was scotoma in both eyes and a slight papilledema, which prompted a CT scan, and so the pneumocephalus was diagnosed.

Treatment of pneumocephalus is mostly managed surgically, especially in a tension pneumocephalus when the pressure has to be alleviated. Once the defect has been found, cartilage, free fascia, and a temporalis muscle fascia flap are used to cover the site.[1] The unique feature of our case is that the pneumocephalus occurred in a completely healthy man without a history of trauma, otologic infection, or otologic surgery. It is our opinion that the cause of the pneumocephalus was forceful Valsalva's maneuver that increased the air pressure in the middle ear and permitted the air to be trapped intracranially through a defect of the tabula interna of the temporal bone. The pneumocephalus was successfully treated surgically, with no recurrence of the phenomenon.

CONCLUSION

Although extremely rare, the occurrence of pneumocephalus should be kept in mind in a patient with a widely pneumatized mastoid complaining of headaches or other nonspecific cerebral symptoms.

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CARCINOMA OF THE ANTERIOR COMMISSURE OF THE LARYNX: I. EMBRYOLOGICAL AND ANATOMIC CONSIDERATIONS

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In this study we attempt to define the organization of the anterior region of the adult larynx, on the basis of its development. For this purpose, we have studied the development of the anterior commissure region on serial sections of human larynges from embryos, fetuses, and adults. Our findings indicate that all the structures of this region derive from a single median mesenchymal band, first evident at 7 to 8 weeks of gestation, between the lateral laminae of the thyroid cartilage. This band of mesenchyme gives rise to all the structures along the midline of the thyroid cartilage and immediately beyond, including the intermediate lamina of the thyroid cartilage, the median process, and the connective tissue that connects the latter with the conoid ligament. We provide, for the first time, evidence that Broyles' ligament (commissural tendon) derives from the dorsal part of the median process and becomes intimately connected with the surrounding structures, including the insertion fibers of the vocal muscles, from early in development. On the basis of this finding we identify an independent anterior commissure region in the adult larynx, which comprises the intermediate lamina, Broyles' ligament, the connective tissue between the Broyles' and conoid ligaments, and the insertion fibers of the vocal muscles. The interpretation of all these structures as a unified region can explain the peculiar progression pathways and evolution of commissural and cordo-commissural tumors.

KEY WORDS — anatomy, anterior commissure, carcinoma, embryology, larynx.

INTRODUCTION

The anterior commissure of the larynx is a transitional zone between the supraglottic and subglottic regions and can be affected by malignant neoplasia. It is rarely the site of origin of commissural tumors, but is quite frequently the point of spreading of tumors that originate in the adjacent laryngeal regions, especially those borne on the vocal cords.

In a previous study,[1] we retrospectively analyzed patients operated on for commissural and cordo-commissural cancers and found no homogeneity of prognosis among tumors that were apparently at the same stage and subjected to the same treatment. We suspected that different relationships of apparently similar tumors to the anterior laryngeal commissure might be the basis of non-uniform clinical evolution among these tumors. However, addressing this issue requires a detailed knowledge of this region. Since the literature on this topic is incomplete and contradictory,[2-7] we have addressed this problem by following the development of the anterior laryngeal commissure in humans.

Very few data are available on this subject from the literature, and data obtained from animals cannot be immediately applied to humans. Simonetta[8] investigated the insertion of the thyroarytenoid muscle in humans and confirmed the existence of a single mesenchymal band in the embryonal larynx that gives origin to the intermediate lamina (IL) of the thyroid cartilage ventrally and to the median process (MP) dorsally. The latter was considered a very thick perichondrium of the IL of the thyroid cartilage. According to Simonetta,[8] the MP is located slightly above the glottic plane and originates independently of the vocal muscles and their insertion fibers. This author did not even mention the possible existence of a tissue equivalent to Broyles' ligament.[2] Since this picture of the anterior region of the larynx cannot explain the diffusion and outcome of many laryngeal tumors, we have investigated this region further, in an effort to give an embryological and anatomic basis to the staging of commissural and cordo-commissural tumors. This last issue will be addressed in part II of this paper.[9]

MATERIALS AND METHODS

This study has been carried out on serial sections of larynges from four embryos, six fetuses, and two adults. More precisely, the four embryos were 7 to 8 weeks old (25 to 30 mm crown-rump); two fetuses were 11 weeks old (43 to 50 mm crown-rump); two fetuses were 20 weeks old (167 to 170 mm crown-rump); and two fetuses were 33 weeks old (310 mm crown-rump). Embryonal and fetal materials came from legal abortions and were apparently free from pathologic malformations of the larynx. Adult material was obtained at surgery for tumors. Specimens

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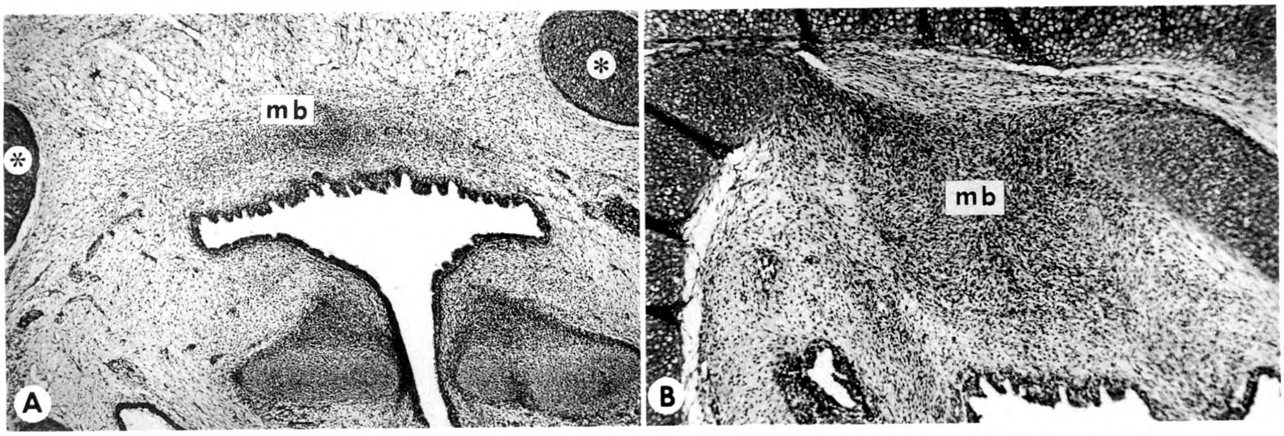

Fig 1. Transverse sections of embryo at 7 to 8 weeks (25 to 30 mm crown-rump). A) Above glottic plane (H & E, original ×125). Anterior margins of lateral laminae of thyroid cartilage are connected by thin band of mesenchyme (mb). Asterisks indicate chondrification nuclei of lateral laminae. B) Same embryo, close to glottis (H & E, original ×250). Mesenchymal band (mb) between lateral laminae is thicker and narrower than at section level of A.

were fixed with 10%, phosphate-buffered formol. Serial sections were stained with hematoxylin and eosin, Van Gieson, and Verhoeff elastic methods. The ethical guidelines of Italian law and the Italian National Medical Council were followed.

RESULTS

Embryos at 7 to 8 Weeks (Crown-Rump Length, 25

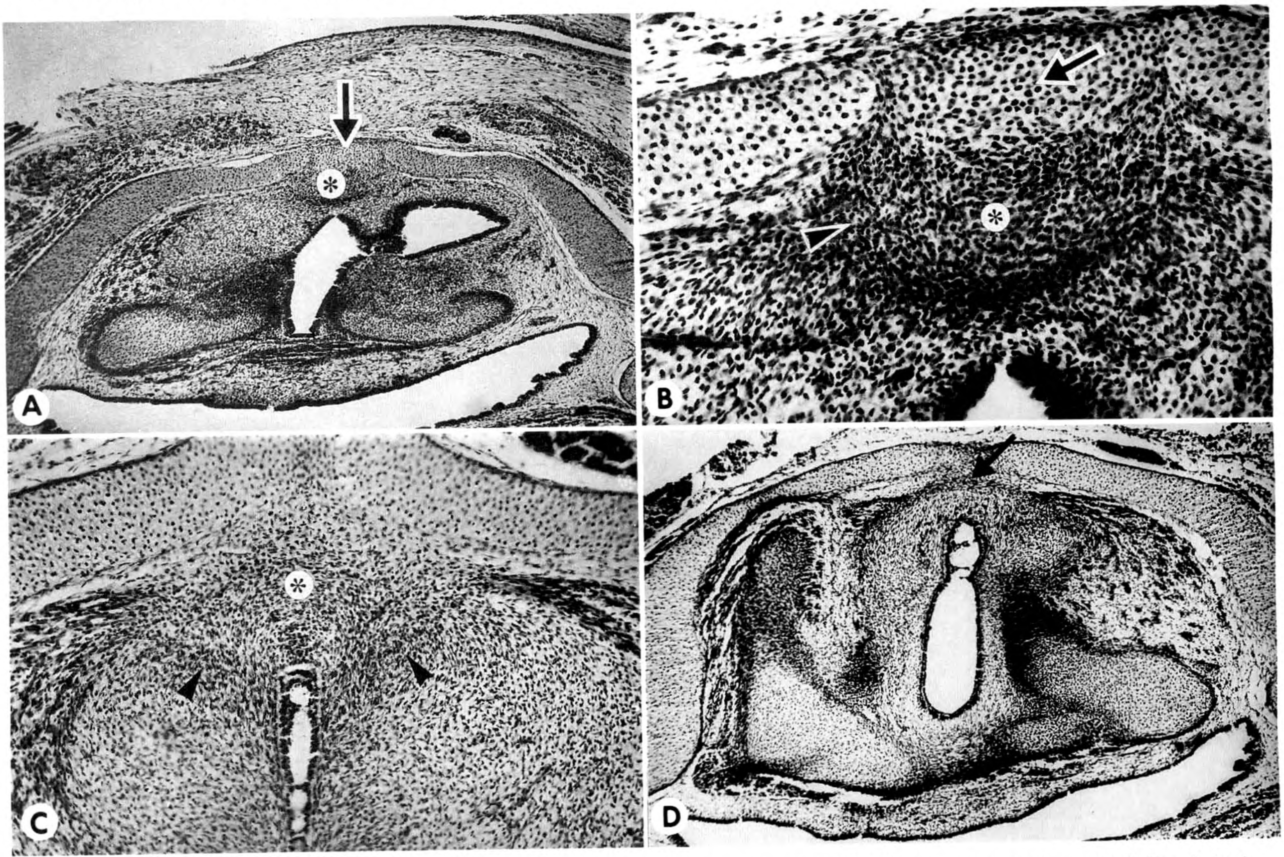

Fig 2. Transverse sections of same fetus at 11 weeks (45 to 50 mm crown-rump). A) Well above glottic plane (H & E, original ×50). Mesenchymal band gives rise, ventrally, to intermediate lamina (arrow) of thyroid cartilage and, dorsally, to median process (asterisk). B) Detail of same section as in A, showing intermediate lamina of thyroid cartilage, surrounded by lateral laminae, and median process (asterisk; H & E, original ×400). Latter contains roundish or fusiform cells oriented parallel to ventrally located intermediate lamina, which is indicated by arrow. Arrowhead on left indicates primordia of insertion fiber of vocal muscle on this side. C) Close to glottic plane (H & E, original ×250). Intermediate and lateral laminae of thyroid cartilage are almost completely fused with each other. Median process (asterisk) shows mesenchymal cells arranged in concentric layers, concave dorsally. Arrowheads indicate primordia of insertion fibers of vocal muscles. D) Below glottic plane (H & E, original ×50). Instead of median process, narrow and thin layer of connective tissue (arrow) is found behind intermediate lamina of thyroid cartilage.

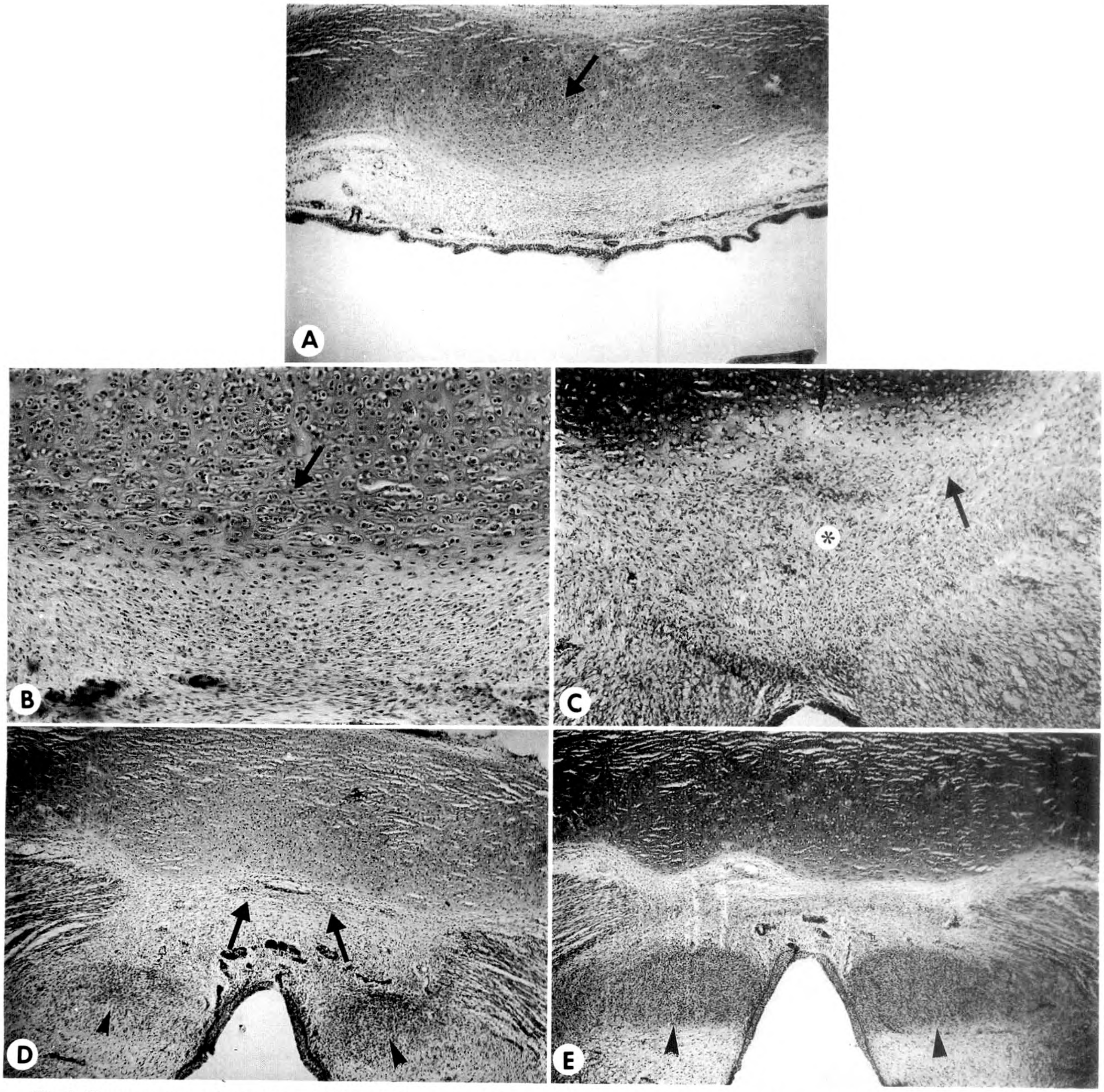

Fig 3. Transverse sections of same fetus at 20 weeks (167 mm crown-rump). A) Above glottic plane (H & E, original ×125). Intermediate lamina of thyroid cartilage (arrow) is connected with lateral laminae, which are thinner than intermediate lamina. B) Detail of same section as in A, which shows two or three layers of chondroblasts arranged parallel to dorsal side of intermediate lamina of thyroid cartilage (arrow; H & E, original ×400). C) Above glottic plane (H & E, original ×200). This section is more caudal than that of A and B. Median process (asterisk) is formed by meshwork of collagen fibers inserting into cartilage of intermediate lamina (arrow). D) Close to glottic plane (H & E, original ×125). Instead of median process, layer of connective tissue including many transverse fibers (arrows) is found behind intermediate lamina of thyroid cartilage at this level. Arrowheads indicate insertion fibers of vocal muscles. E) Below glottic plane (H & E, original ×125). At this level, mucosal epithelium and lamina propria appear separated from intermediate lamina of thyroid cartilage by thin layer of loose connective tissue. This tissue is continuous with thyroarytenoid muscles and lateral lamina perichondrium and is derived from median mesenchymal band recognized at 7 to 8 weeks. Arrowheads indicate insertion fibers of vocal muscles.

to 30 mm). At this stage the two lateral laminae (LL) of the thyroid cartilage are undergoing chondrification, and their anterior margins are connected with each other by a band of mesenchyme that extends for the entire length of the thyroid cartilage, down to the more cephalic portion of the subglottic region. This band of mesenchyme is flanked by the mesenchyme of the future vocal cords laterally, and caudally is continuous with that of the subglottic region. It is broader and thinner in the cranial portion of the larynx, in which the two chondrification nuclei of each of the LL are still separated from each other (Fig 1A), and narrower and thicker in the caudal portion of the larynx (ie, glottic-subglottic region), in which the

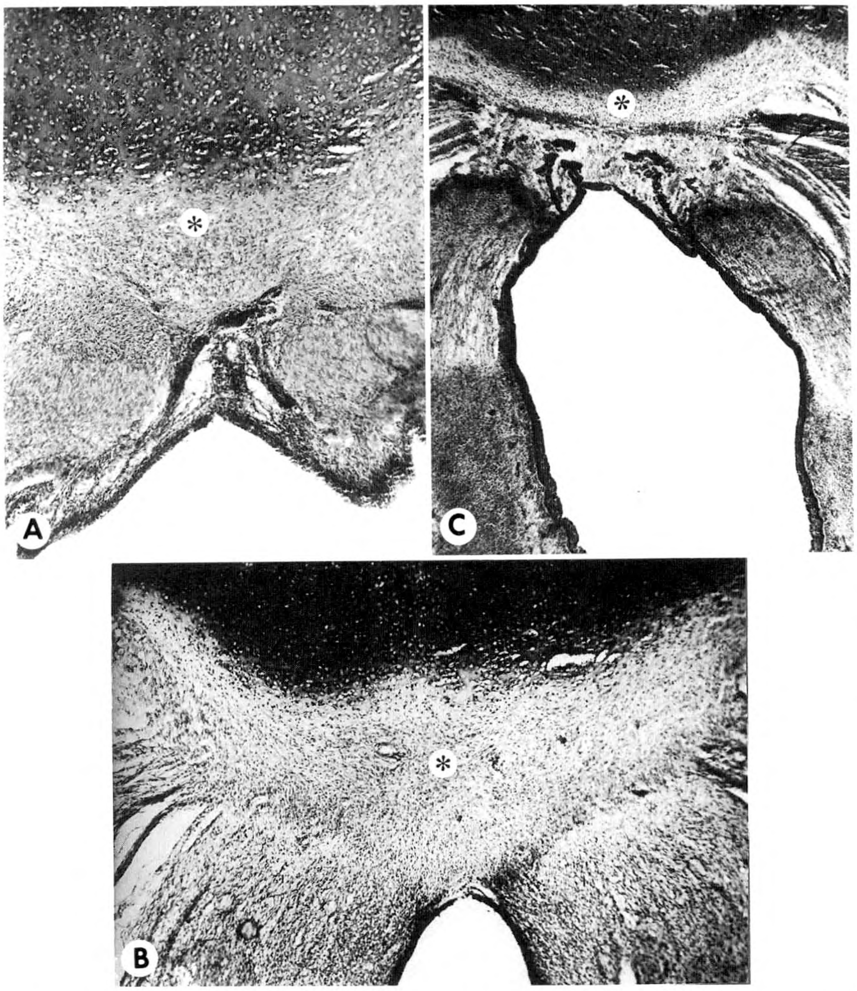

Fig 4. Transverse sections of same fetus at 33 weeks (310 mm crown-rump; H & E, original ×125). A,B) Section of A is more cranial than that of B. Median process (asterisk) is transforming into Broyles' ligament and plays role of perichondrium for intermediate lamina of thyroid cartilage; it is continuous with insertion fibers of vocal muscles. C) Below glottic plane. Asterisk indicates dense connective tissue that is present at this level behind intermediate lamina of thyroid cartilage, in place of median process. Many vessels and glands are shown in lamina propria.

LL are in a more advanced stage of chondrification (Fig 1B).

Fetuses at 11 Weeks (Crown-Rump Length, 43 to 50 mm). The ventral part of the above-described band of mesenchyme differentiates into the IL of the thyroid cartilage, whereas its dorsal part, as a mesenchyme, forms the MP (Fig 2A), which will further develop as described below. The chondrification of the IL starts from a median nucleus and proceeds until the cartilage becomes continuous with the LL and the whole thyroid cartilage is complete. The MP is rich in roundish or fusiform cells, which are oriented parallel to the IL ventrally (Fig 2B), and in hemicylindrical layers, concave dorsally and concentric to each other dorsally (Fig 2C). The insertion fibers of the vocal muscles appear to end up in the dorsal part of the MP (Fig 2B). The MP is narrower (in a laterolateral direction) and thicker (in a ventrodorsal direction) at its cranial end than at the caudal end. At the glottic plane it ends abruptly and is followed by mesenchyme, which is narrow and thin at first and then becomes progressively broader and thicker down to the inferior margin of the thyroid cartilage, where it becomes continuous with the fibers of the future conoid ligament, which are undergoing differentiation (Fig 2D). Despite the close relationships to the surrounding structures, the MP is always sharply distinct from them, ie, from the IL of the thyroid cartilage ventrally, the differentiating laryngeal muscles laterally, and the primordia of the insertion fibers of the vocal muscles dorsally. The elastic vocal nodule will differentiate within these insertion fibers.

Fetuses at 20 Weeks (Crown-Rump Length, 167 mm). The IL is almost completely joined to the LL, but is still distinguishable from the latter for its greater thickness (Fig 3A). The MP extends down to immediately above the glottic plane. It is continuous with the perichondrium of the LL and is as broad as, but thinner than, the IL. At the border between the MP and IL there are two or three layers of round-shaped cells with basophil cytoplasm, which may be interpreted as chondroblasts and are interspersed with bundles of collagen fibers (Fig 3B). The bulk of the MP is a dense, three-dimensional meshwork of bundles of collagen fibers containing many fibroblasts and inserted into the cartilage of the IL (Fig 3C). Imme-

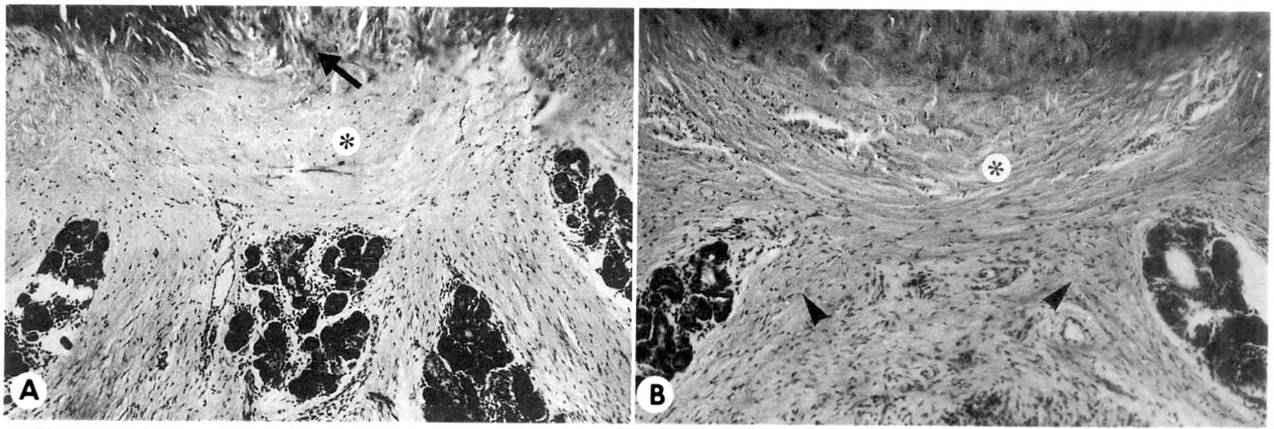

Fig 5. Transverse sections of same adult larynx (H & E, original ×125). A) Above glottic plane. Intermediate lamina of thyroid cartilage (arrow) is bordered dorsally by Broyles' ligament (asterisk). This ligament appears virtually devoid of vessels and continuous with dorsal surface of intermediate lamina. B) Close to glottic plane. Connection between Broyles' ligament (asterisk) and insertion fibers of vocal muscles (arrowheads) at this level resembles Greek letter χ, which corresponds to so-called X space of Bagatella and Bignardi.[6,7]

diately above the glottic plane, the fibers of the MP become continuous with the insertion fibers of the vocal muscles, which are at present made up of a loose, cell-rich connective tissue (Fig 3C). The MP fibers are also continuous with each other in the glottic plane. At this time, the MP is delimited as follows: 1) dorsally, by the insertion fibers of the vocal muscles and more caudally by the laryngeal mucosa in which glands and vessels are differentiating; 2) laterally, by the thyroarytenoid muscles, which are differentiating; and 3) ventrally, by the IL.

The MP is not recognizable caudal to a level immediately above the glottic plane (Guerrier's "plane zero," cited by Andrea[5]) (Fig 3D). Caudal from this level, the mucosa is separated from the IL of the thyroid cartilage by two layers of connective tissue (Fig 3E): a thin, loose, dorsal one, which is apparently correlated with the lateral thyroarytenoid muscles, and a ventral, dense one, which behaves as a perichondrium for the IL and is continuous with the perichondrium of the LL and with the conoid ligament. This layer of perichondrium of the IL appears to derive from the median mesenchymal band, recognized at 7 to 8 weeks.

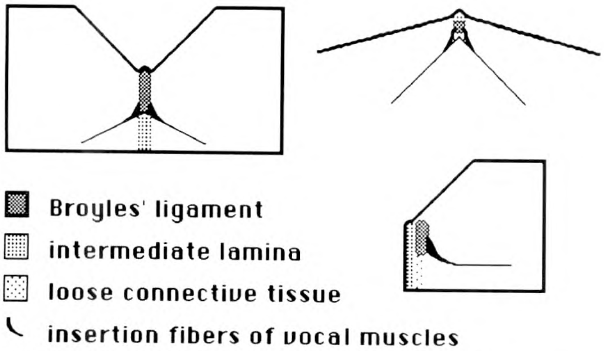

Fig 6. Diagram illustrating structures deriving from mesenchymal band between primordia of lateral laminae of thyroid cartilage, and their relationships to insertion fibers of vocal muscles.

Fetuses at 33 Weeks (Crown-Rump Length 310 mm). The IL is fused with the LL, but is thicker than them in its median portion, so that its dorsal surface is convex (Fig 4A).

The MP, in transverse section, has an irregular triangular shape with the tip toward the glottis margin and the base toward the IL. This triangle is progressively wider in a cephalocaudal direction. The ventral portion of the MP is a chondrogenic layer for the IL of the thyroid cartilage, whereas its dorsal, thicker portion is made up of a cell-rich, dense connective tissue containing few vessels. This tissue is continuous, dorsally, with the insertion fibers of the vocal muscles (Fig 4B). The connective cells and fiber bundles of this dorsal part of the MP are oriented in part on a horizontal plane — some parallel and some perpendicular to the surface of the IL — and in part are oblique in a lateromedial, dorsoventral, and caudocephalic direction. The orientation of fiber bundles suggests that the MP forms Broyles' ligament.[1,2] The dorsal surface of the MP is marked by a layer of cell-rich, loose connective tissue that represents, as at 20 weeks, the insertion fibers of the vocal muscles.

The MP ends immediately above the glottic plane and is followed by a relatively thin layer of dense connective tissue that borders the IL in continuity cranially with the MP and caudally with the conoid ligament. Collagen fibers of this tissue insert into the cartilage of the IL, and from the histologic standpoint, this tissue can be considered as a perichondrium of the IL (Fig 4C). Muscle fibers, continuous with the lateral thyroarytenoid muscles, are differentiating between this dense tissue and the lamina propria of the mucosa. On the glottic plane and caudally, the lamina propria of the laryngeal mucosa is wider and richer in vessels than it is cranially to that plane, and contains glands.

Adults. The IL is thicker from the superior thyroid notch to immediately above the glottic plane, than it is on this plane and caudally. The dense connective tissue that corresponds to the MP described in embryos and fetuses is continuous from the IL ventrally to the lamina propria of the laryngeal mucosa dorsally and laterally (Fig 5A). In transverse section, it has the same shape as the MP in fetuses at 33 weeks and is rich in elastic fibers. Isolated collagen fibers and bundles of fibers, close to the dorsal surface of the IL, penetrate into the latter. More dorsally, the bundles of collagen fibers run along the same directions as described for the MP in fetuses at 33 weeks and, dorsally, merge with the insertion fibers of the vocal muscles. Immediately above the glottic plane, those fibers that run parallel to the IL, together with the insertion fibers of the vocal muscles, give rise to a sort of chiasma (so-called X space of Bagatella and Bignardi[6,7]; Fig 5B). All the dense connective tissue that derives from the MP dorsal to the IL forms a connective system between the latter and the insertion fibers of the vocal muscles, and corresponds to the so-called Broyles' ligament.[1,2] This ligament appears devoid of glands and contains scarce vessels, whereas these structures are present in the surrounding lamina propria of the laryngeal mucosa, more numerous on the glottic plane and caudally than above that plane.

DISCUSSION

Our findings indicate that a single mesenchymal band, well-developed already at 7 to 8 weeks of gestation, gives rise to all the structures along the midline of the thyroid cartilage and immediately behind, therefore including the IL, the MP, and the fibrous tissue that connects the latter with the conoid ligament.

The MP differentiates into Broyles' ligament or the commissural tendon, which remains tightly connected with the IL; fibers from this ligament penetrate deeply into the IL and therefore this ligament behaves like a perichondrium for the dorsal surface of this lamina. The caudal end of this ligament is immediately above the glottic plane. We conclude, on the basis of our embryological observations, that Broyles' ligament is an integral part of the commissure region.

The differentiating insertion fibers of the vocal muscles become strictly connected with the MP starting very early in development (11 weeks); this connection is maintained and reinforced by Broyles' ligament. Therefore, we suggest that the insertion fibers of the vocal muscles be included in the commissure region.

In conclusion, the anterior commissure region can be defined, anatomically, as made up of the IL, Broyles' ligament, the connective tissue between the Broyles' and conoid ligaments, and the insertion fibers of the vocal muscles (Fig 6).

This interpretation of the anterior commissure region is reinforced by clinical data: tumors arising in the cordo-commissural region rarely invade cranially to the glottic plane, where they should infiltrate the thick, poorly vascularized and gland-free Broyles' ligament and adjoining cartilage. Rather, these tumors are stopped by the basket-like fibrous structure formed by the caudal end of Broyles' ligament together with the thyroid cartilage and the insertion fibers of the vocal muscles. These same tumors more frequently invade the loose blood vessel–rich and gland-rich tissue caudal to the glottic plane, down toward the conoid ligament; should they perforate the thyroid cartilage (an unusual event), they would do so immediately below the caudal end of Broyles' ligament, where the laryngeal mucosa is next to cartilage (Guerrier's so-called "plane zero").

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DEMONSTRATION OF THE NASAL SEPTAL BRANCHES OF THE SPHENOPALATINE ARTERY BY USE OF A NEW INTRAVASCULAR INJECTION METHOD

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We injected a new injection material into the external carotid artery using a new method, which led to the successful demonstration of the nasal septal branches of the sphenopalatine artery in human cadavers. The result shows the trunk of the artery divided into three main branches, the upper two of which run toward Little's area. We believe that the knowledge of septal branches, shown in a photograph, is very useful, not only for nasal treatment, but also for anatomic demonstration to students.

KEY WORDS — epistaxis, Kiesselbach's area, Little's area, nasal septum.

INTRODUCTION

Epistaxis usually rises from the anteroinferior part of the nasal septum,[1] known as Little's area[2,3] or Kiesselbach's area.[4] The trunk of septal branches of the sphenopalatine artery (one of the branches of the maxillary artery from the external carotid artery) passes across the anterior aspect of the sphenoid bone. It then descends diagonally down the septum toward Little's area, to anastomose with branches of the superior labial artery from the external carotid artery (via the facial artery), the greater palatine artery (branching from the maxillary artery), and the anterior ethmoidal artery from the internal carotid artery (via the ophthalmic artery).[5] The demonstration of the territories of the nasal septal arteries is very important for the treatment of epistaxis and for its surgery. We could find several schemata of the nasal septal arteries,[5-8] but no actual figure of them. So, we tried to illustrate the arteries on the nasal septum by use of a new intravascular injection method.[9]

MATERIAL AND METHODS

For anatomic dissection three cadavers were used, which had been placed shortly after death in coffins filled with dry ice to minimize the postmortem changes until they were put into a cold chamber at 4°C. Twenty-four hours after death, the cadavers were injected and circulated with 4.0% formaldehyde into the arterial system for approximately 1 hour by use of an intermittent pulsation pump for fixation, after opening the bilateral internal jugular and femoral veins to drain blood.

Injection Material. For the new injection material,[9] we prepared a mixed solution with polyvinyl acetate (15% in volume) as the main component, blue acrylic color (1.2%) as the dye material, and methyl alcohol (81.8%) as the solvent. Several unique characteristics of the injection material will be mentioned in Discussion.

Injection Method. The external carotid artery of only one side (right or left) was selected for the injection. The injection material containing the blue dye was injected through an L-shaped metal tube that was inserted into the cervical portion of the external carotid artery prior to the anatomic dissection. For the injection, a tubing pump system (Cole-Parmer Masterflex, model 7520-10) composed of a motor, a rotary pump head, and a silicone tube was employed. One end of the tube was connected to the L-shaped metal tube and the other end was inserted into a bottle containing the injection material. The material was injected into the external carotid artery at a pressure of 100 to 140 mm Hg.

After removal of the brain, the head (skull base and

RESULTS OF INTRAVASCULAR INJECTION TO SEPTAL ARTERIES

Subject	*Age*	*Sex*	*Septal Height (mm)*	*Septal Width (mm)*	*Stain of SPA*	*Stain of GPA*	*Stain of SLA*
1	69	F	45	68	+	+	–
2	74	M	47	65	+	+	+
3	58	M	48	69	+	–	+

Septal height — vertical diameter of nasal septum, corresponding to "a" of Fig 2, septal width — horizontal diameter of nasal septum, corresponding to "b" of Fig 2, SPA — branches of sphenopalatine artery, GPA — branches of greater palatine artery, SLA — branches of superior labial artery, + — visible, – — invisible.

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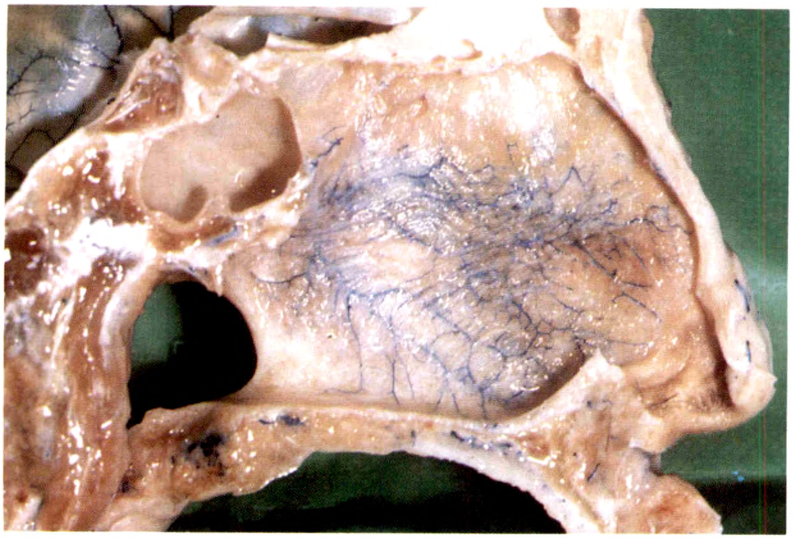

Fig 1. Septal branches of sphenopalatine artery (subject 1).

face) was sagittally cut into two halves at a plane 5 to 10 mm off from midsagittal toward the injection side. A portion of the nasal septum was dissected to demonstrate the septal arteries filled with the injection material. The mucous membrane of the septum was peeled to elucidate its arteries.

RESULTS

The age, sex, vertical and horizontal diameters of the septum, and colored state of the three branches are listed in the Table. The external carotid artery via the maxillary artery can be divided into branches such as the sphenopalatine, the greater palatine, and the superior labial artery. In subject 1, we observed that the sphenopalatine artery gave off three septal branches at the anterior surface of the sphenoid bone: the two upper ones ran toward Little's area, and the other, toward the basis of the septum, anastomosed with the branch of the greater palatine artery. A number of twigs derived from each branch and anastomosed with each other. The superior labial artery was not found. In subject 2, although we observed three septal branches of the sphenopalatine artery, the branches toward the basis of the septum were too narrowly distributed to anastomose with the branches of the greater palatine artery. We found a short branch of the superior labial artery at the upper site of the nasal vestibule covered with skin. In subject 3, we also observed three septal branches of the sphenopalatine artery: two toward Little's area and the remaining toward the basis of the septum. However, all of them broke off on the way and did not anastomose with each other. One branch of the superior labial artery ran toward the branch of the sphenopalatine artery. We found that the sphenopalatine artery gave three main septal branches: the upper two running toward Little's area, the other toward the basis of the septum in the three subjects. We obtained a good picture of the nasal septal branches in subject 1 (Figs 1 and 2).

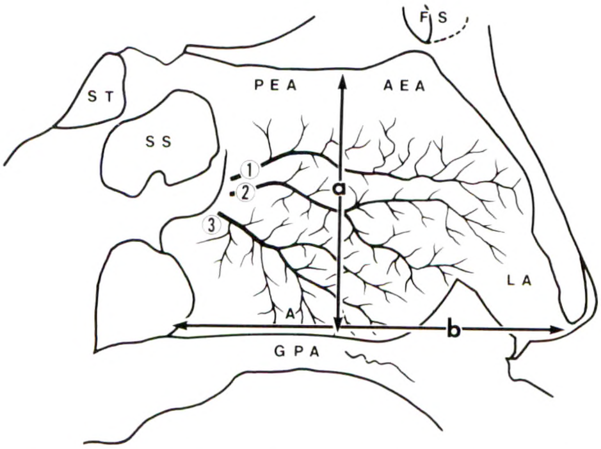

Fig 2. Line drawing of Fig 1. 1, 2, 3 — three main septal branches of sphenopalatine artery, A — anastomoses with septal branches of sphenopalatine artery and branches of greater palatine artery, AEA — anterior ethmoidal artery supplying area, FS — frontal sinus, GPA — greater palatine artery, LA — Little's area, PEA — posterior ethmoidal artery supplying area, SS — sphenoidal sinus, ST — sella turcica, a — vertical diameter of nasal septum, b — horizontal diameter of nasal septum.

DISCUSSION

The injection material has several unique characteristics: 1) its fluidity is about the same as that of methyl alcohol; 2) the size of the dye particles is fine enough to fill the small arteries with the colored material to show them clearly; and 3) the injection material hardens immediately after being sprinkled with water or sinking in the fixative containing water, so that the surrounding area is not unnecessarily stained by the overflowed injection material.

Precise knowledge of the nasal septal branches of

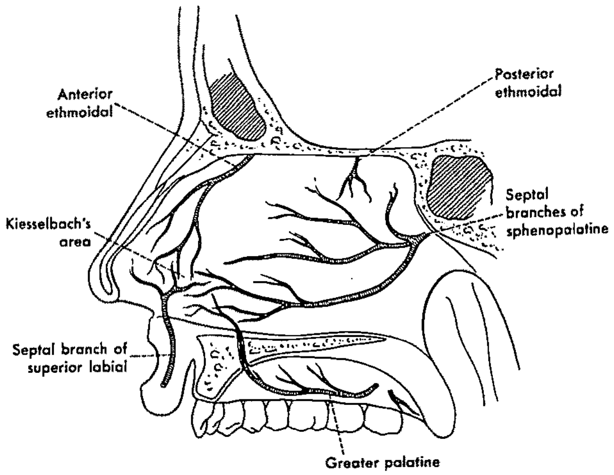

Fig 3. Illustration of arteries of nasal septum. (Reprinted with permission.[6])

the sphenopalatine artery is particularly important when nasal bleeding from the septum is treated. It is said that the lower nasal septal branch of the sphenopalatine artery makes an arc as it runs to Little's area, shown by the line drawing of arteries of the septum[5,6] (Fig 3[6]). However, we found that there were three main septal branches of the sphenopalatine artery: the upper two ran toward Little's area, and the other ran down toward the basis of the septum (Figs 1 and 2). As Fig 1 shows, we found that there are no injected arteries in the upper third of the septum. The arteries in this area were considered to branch from the anterior and posterior ethmoidal arteries. There were no injected vessels in Little's area, because it was full of capillaries, and the injected material was hardened before reaching there. Several textbooks of otolaryngology contain line drawings to illustrate the blood supply to the nasal septum.[5,7,8] We found only one x-ray figure of branches from the nasopalatine artery,[10] and could not clearly distinguish the arteries supplying the nasal septum from other arteries.

We have learned by experience that the effective treatment of arterial hemorrhage from the anteroinferior part of the nasal septum is electrocauterization at the posterosuperior point of a bleeding site of Little's area. This effectiveness of electrocauterization corresponded to our findings on the blanching route of the sphenopalatine artery, ie, our finding that the upper two branches ran toward Little's area. The demonstration of the septal branches of the sphenopalatine artery by use of the new injection method should be useful in treatment of septal bleeding, and should be helpful in teaching rhinological anatomy.

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EVALUATION AND MANAGEMENT OF THE LINGUAL THYROID GLAND

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Lingual thyroid gland is a rare clinical entity that is due to failure of descent of the gland anlage early in the course of embryogenesis. It may present with symptoms of dysphagia, upper airway obstruction, or even hemorrhage at any time from infancy through adulthood. We present two illustrative cases of lingual thyroid gland along with a protocol for diagnosis and management of the condition. Elements in the diagnostic and therapeutic evaluation are described with attention to the clinical findings, laboratory tests, and radiographic imaging studies employed in confirming the diagnosis and planning appropriate treatment. The natural history of the condition is reviewed and a treatment strategy is outlined that focuses on the use of suppressive doses of thyroid hormone as the initial therapy. Surgical excision of the gland is reserved for more advanced cases of gland enlargement resulting in airway compromise, severe dysphagia that limits oral intake, or ongoing hemorrhage.

KEY WORDS — ectopic thyroid, lingual thyroid.

INTRODUCTION

Lingual thyroid is the term applied to a mass of ectopic thyroid tissue located on the base of the tongue in the midline. It may be found anywhere between the circumvallate papillae and the epiglottis. It is believed to be caused by developmental anomalies involving the descent of the embryologic gland anlage from its position posterior to the tuberculum impar to its normal pretracheal location. This typically occurs between week 3 and week 7 of embryologic development. Thyroid tissue may be deposited in any position along this early thyroglossal tract. Ectopic thyroid tissue has also been reported in midline locations, including the oropharynx,[1] infrahyoid region,[2] larynx and trachea,[3] mediastinum,[4] esophagus,[5] and heart.[6]

The pathogenesis of the condition remains unclear, although it has been postulated that maternal antithyroid immunoglobulins may cause arrest of gland descent and predispose to poor gland function later in life.[7] Lingual thyroid is found in approximately 1 in 100,000 people, and affected individuals have no other thyroid tissue in 70% to 100% of cases.[8-10] There is a marked female sex predominance, with a female to male ratio of 4:1 to 7:1.[5,6,9-11] Clinical evidence of hypothyroidism is found in up to 33% of cases.[8-10] Most lingual thyroid glands contain histologically normal tissue, but there are rare reports of carcinoma arising within a lingual thyroid.[12,13]

The potential for malignant degeneration in a lingual thyroid appears to be the same as for orthotopic thyroid tissue, although the report of carcinoma originating in a lingual thyroid gland is an exceptionally rare event.[14,15] There have been 21 cases of carcinoma in a lingual thyroid reported to date, and 95% of these were papillary carcinoma. Among these cases there was an equal sex distribution, and the age at presentation ranged from 12 to 74 years.[15] The incidence of thyroid disease among family members of lingual thyroid patients is higher than in the population at large.[16]

CASE REPORTS

Case 1. An 8-year-old girl was referred to the otolaryngology clinic at Lincoln Medical and Mental Health Center with a history of chronic cough and throat clearing. She was also noted to have mild dysphagia to solid foods that was felt to be worsening. She had no other known medical problems and no prior surgery. A first-degree female relative was known to have multinodular goiter.

On physical examination the child was noted to have a 2 × 2.5 × 1.5-cm mass in the tongue posterior to the circumvallate line. It was smooth, pink, and without evidence of hemorrhage or ulceration. There

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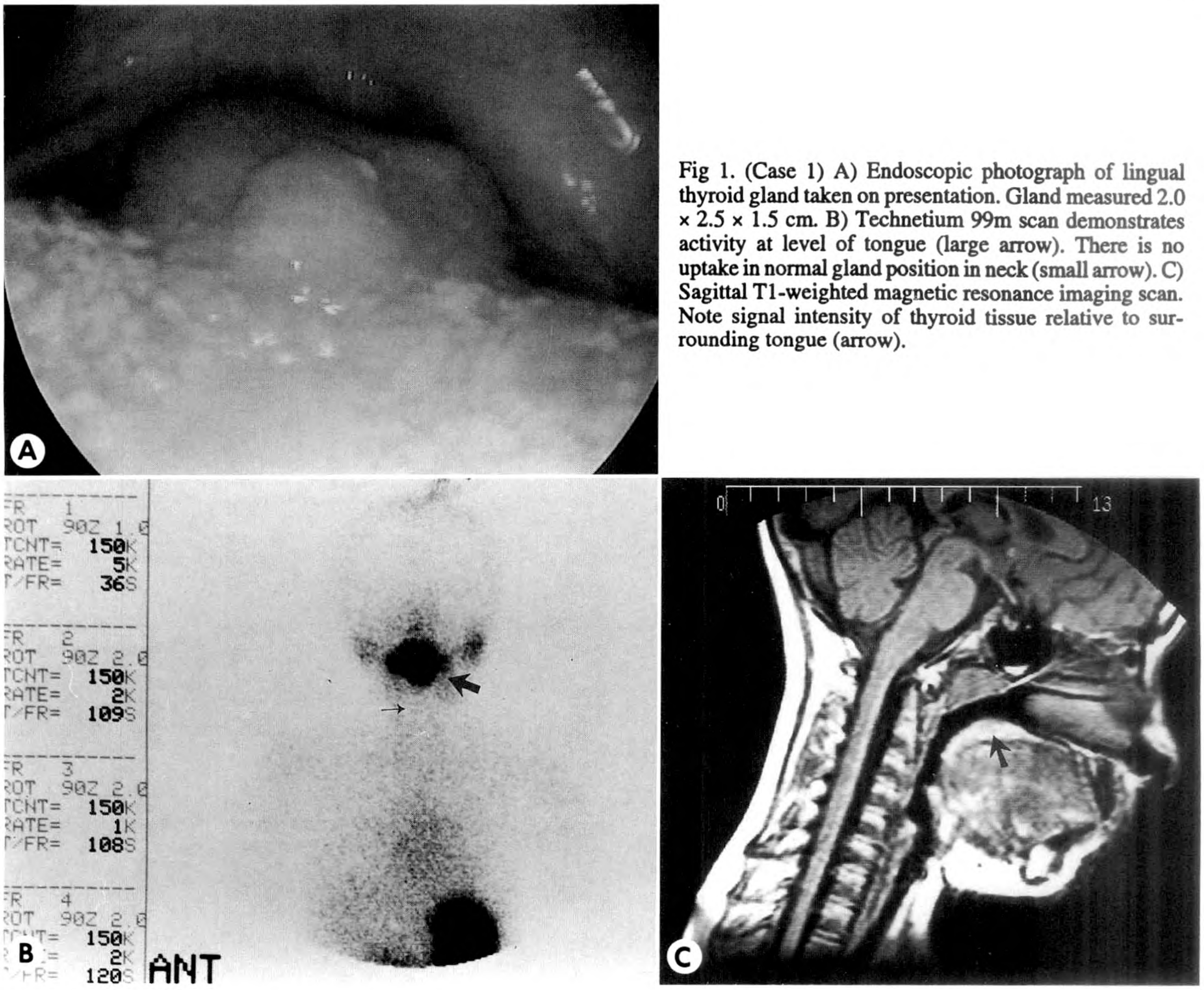

Fig 1. (Case 1) A) Endoscopic photograph of lingual thyroid gland taken on presentation. Gland measured 2.0 × 2.5 × 1.5 cm. B) Technetium 99m scan demonstrates activity at level of tongue (large arrow). There is no uptake in normal gland position in neck (small arrow). C) Sagittal T1-weighted magnetic resonance imaging scan. Note signal intensity of thyroid tissue relative to surrounding tongue (arrow).

was no associated stridor or hoarseness. Examination of the neck revealed no palpable thyroid tissue in the normal pretracheal position. The lingual gland was photographed on presentation with a 0° rigid endoscope (Storz Hopkins) and a video camera system with instant printing capability (Sony Corp). This was easily tolerated and provided near-total visualization of the gland (Fig 1A). Thyroid function tests demonstrated normal thyroxine (T4) and triiodothyronine (T3) with an elevated thyroid-stimulating hormone (TSH) level of 4.0 micro–international units per milliliter (μIU/mL; normal range, 0.3 to 2.0 μIU/mL). Additional testing included a technetium (Tc 99m) thyroid scan that showed concentrated isotope uptake in the area of the tongue without any uptake in the normal thyroid position (Fig 1B).

A diagnosis of lingual thyroid was made and the patient was started on suppressive therapy of daily doses of 0.1 mg of L-thyroxine. Repeat thyroid function tests performed 1 month later showed suppression of TSH below 0.1 μIU/mL at this time.

The patient was then followed over the course of a year and was noted to have progression of her dysphagia symptoms, including decreased oral intake and a persistent foreign body sensation in the throat despite continued suppression therapy. The TSH level was once again elevated to 4.5 μIU/mL. To counter this, the dose of T4 was increased to 0.15 mg to further suppress the TSH level and halt progression of gland enlargement. A magnetic resonance imaging (MRI) scan was obtained (Fig 1C), as well as additional endoscopic photographs, to further assess gland size and airway status. The gland enlargement halted again in response to successful thyroid suppressive treatment, and the symptoms subsided. She has been followed clinically for 3 years, including scheduled monthly examinations in conjunction with periodic endoscopy and photography of the gland to monitor its size and overall airway patency. To date she has not required surgical intervention.

Case 2. A 34-year-old man presented to the otolaryngology clinic at The New York Eye and Ear Infirmary complaining of a sore throat that had been present for more than a year. He denied any difficulty

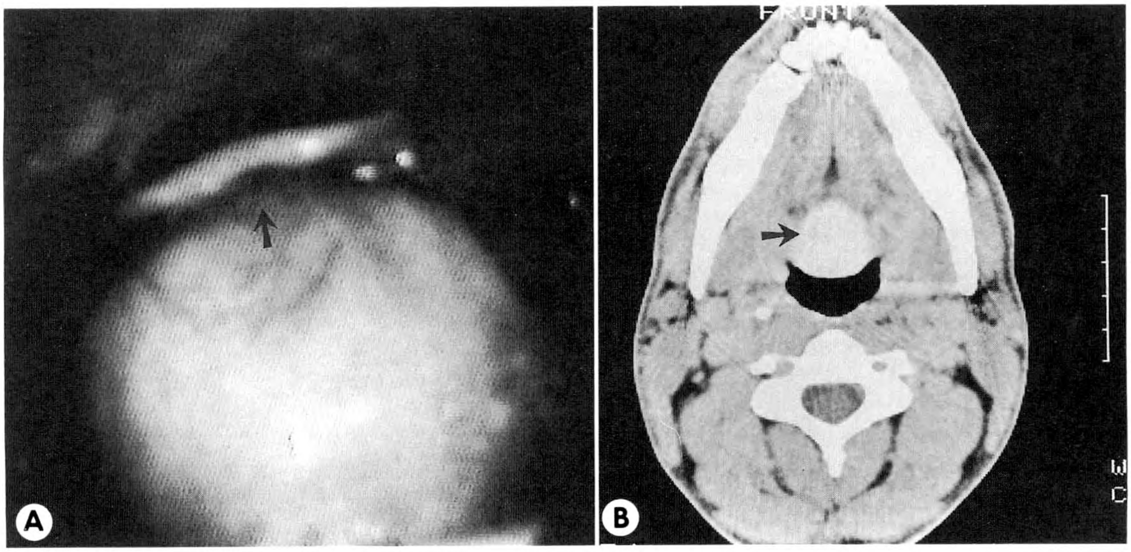

Fig 2. (Case 2) A) Endoscopic photograph of lingual thyroid gland. Note prominent superficial blood vessels and position of epiglottis (arrow). Measurements were 2.5 × 2.0 × 2.0 cm within tongue base. B) Noncontrast axial computed tomogram demonstrates lingual thyroid tissue present within tongue base (arrow). Note natural enhancement of thyroid tissue. Dimensions of gland are approximately 2.5 × 2.5 cm.

breathing or swallowing food.

Physical examination was significant for a raised, red-colored tongue mass located 2 cm posterior to the circumvallate papillae. Several large blood vessels could be seen on its surface when viewed with the 0° rigid endoscope. Endoscopic photographs were taken at this time to document gland size, which measured 2.5 × 2.0 × 2.0 cm (Fig 2A). There was no palpable thyroid gland in the normal position in the neck. The remainder of the examination findings were normal. Thyroid function tests were found to be within normal limits. A Tc 99m scan showed marked uptake in the tongue base and no uptake in the normal thyroid position in the neck.

The patient was informed of the nature of his condition and was offered a course of suppressive therapy with L-thyroxine, which he refused. He was then temporarily lost to follow-up until 8 months later, when he returned with a 1-week history of intermittent bleeding from the mouth. A repeat endoscopic examination was performed that showed some enlargement of the gland, erosion of the surface vessels, and evidence of recent hemorrhage. A computed tomography (CT) scan was obtained (Fig 2B) that showed the full extent of the gland within the tongue base, as well as the size of the airway.

The option for surgical excision of the gland was discussed with the patient, including the need for temporary tracheostomy and long-term postoperative thyroid hormone replacement. He agreed to the procedure and underwent total gland excision via a transhyoid approach. He was decannulated on the fourth postoperative day and was discharged home, tolerating a soft diet on the following day. He has been followed for a year since his surgery and remains free from throat pain without further episodes of bleeding. He is currently maintained on a daily dose of 0.1 mg L-thyroxine. Thyroid function tests performed during 3- and 6-month follow-up visits revealed normal T3 and T4 levels with a TSH level of less than 0.1 μIU/mL.

DISCUSSION

The initial evaluation of lingual thyroid is based on those symptoms that bring it to the attention of the otolaryngologist. These symptoms relate to oropharyngeal obstruction and include dysphagia with or without decreased oral intake, dysphonia, dyspnea, and hemorrhage.[6,16] Stridor may also be present at any time after birth, but is most common in the neonate.[17] Lingual thyroid is felt to have two main clinical presentations that are based on the patient's age at onset of symptoms.[9,16] One group consists of infants and young children whose lingual thyroid is detected on routine screening. Often these patients suffer from failure to thrive and mental retardation. The second group presents with the onset of symptoms of dysphagia and oropharyngeal obstruction before or during puberty. Hypertrophy of the gland occurs in response to the elevation in TSH levels generated by the increased metabolic demand for thyroid hormone present during puberty.[18] A similar effect is seen in other states of metabolic stress, such as pregnancy, trauma, infection, and menopause.[18]

The initial evaluation includes a thorough head and neck examination. Attention is paid to visualiz-

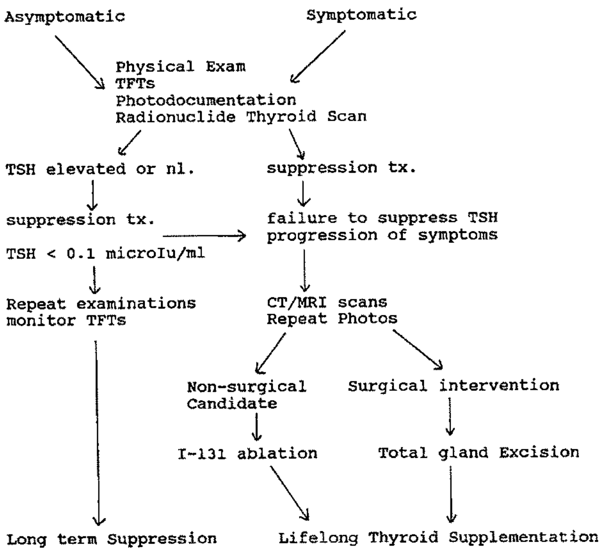

Fig 3. Management protocol. TFTs — thyroid function tests, TSH — thyroid-stimulating hormone, nl. — normal, tx. — therapy.

ing the oropharynx, as a lingual thyroid gland typically appears as a raised mass posterior to the circumvallate papillae. It may range from light pink to bright red or blue, and the surface may be smooth or irregular. Hemorrhagic changes may be present, with frank ulceration and bleeding sometimes encountered.[8,9] Endoscopic evaluation of the upper airway is necessary to determine gland size and airway patency and to visualize the larynx for other possible anomalies such as hemangioma, vallecular cyst, or hypertrophied lingual tonsil.[16] Photodocumentation of gland size and position can be done at this time via rigid or flexible endoscopy. Palpation of the neck is done to check for the presence of thyroid tissue in the normal pretracheal position.

Laboratory studies focus on thyroid function tests that are obtained on presentation. These often demonstrate normal to marginal gland function with normal to decreased levels of T3 and T4 and elevated levels of TSH and thyroglobulin.[18,19]

Radiologic imaging studies are indispensable in the evaluation of ectopic thyroid. Technetium scanning should be performed to confirm the clinical diagnosis. This typically shows radionuclide activity at the level of the mouth, with no demonstrable activity in the normal position in the neck. This method fully avoids the need for diagnostic biopsy.[6] Computed tomography provides an accurate method of demonstrating gland size and may often be performed without contrast, as the thyroid naturally accumulates iodide.[20] In cases of marked gland hypertrophy, sagittal reconstructions are useful in visualizing the depth of the gland within the tongue base and overall airway patency. Magnetic resonance imaging represents a new modality for assessing gland size and position.[11] Unlike CT scanning, it avoids exposure to ionizing radiation and produces excellent sagittal views of the ectopic gland and surrounding tissues with T1-weighted and proton density images.[11]

A role for ultrasound examination of a lingual thyroid gland has yet to be firmly established. Depending on the skill of the sonographer, it could possibly reveal details of the consistency of the gland and any possible nodules or cysts contained within it. This would aid in identifying and following an enlarging component of a lingual gland without the need for additional ionizing radiation.

The clinical management of lingual thyroid remains somewhat controversial.[18,21] The presence or absence of symptoms provides the best initial guide to treatment (Fig 3). The use of suppressive therapy with exogenous thyroid hormone is the mainstay of medical management. The goal of therapy is to suppress TSH and thereby remove the stimulus for gland enlargement. This approach is mandatory for symptomatic patients and those asymptomatic patients with elevated TSH levels. It also seems warranted in asymptomatic euthyroid patients in an effort to prevent the hypothyroid state that eventually develops in most cases and leads to hypertrophy of the gland. Thyroid function is then monitored at regular intervals, ideally every 3 months or less. This is combined with ongoing clinical examinations while the patient is on suppressive therapy. This regimen provides control of gland size and resultant symptoms in most patients.[21,22] If the patient remains euthyroid, without evidence of gland enlargement, the follow-up visits can be maintained at 3-month intervals throughout the first year of suppressive therapy. More frequent examinations should be resumed during periods of metabolic stress such as puberty or pregnancy.

Surgical intervention is necessary for selected patients who become symptomatic or have worsening of their initial symptoms while on suppressive therapy. Surgery becomes crucial under conditions such as severe or repeated hemorrhage, gland enlargement with dysphagia that prevents adequate oral intake, and significant airway compromise or dysphonia. When surgery is contemplated, CT or MRI scans are helpful in determining the best surgical approach for total gland excision. The suprahyoid and transhyoid methods provide excellent access for the majority of cases and avoid the limited exposure of the transoral route and the added morbidity of a mandible and tongue splitting procedure. Preoperative tracheostomy and nasotracheal intubation are both effective in securing an airway at the time of surgery. The decision to use one of these modalities in favor of another depends on the preference of the surgeon and the availability of an intensive care unit setting in which to manage a sedated and intubated patient until postoperative edema resolves. Total surgical excision of the gland is necessary to avoid later hypertrophy of residual tissue. There is little to no risk of postoperative hypocalcemia, as the parathyroid glands arise from the third and fourth branchial arches, follow a different path of embryonic descent, and are still found in their normal positions in the neck.[23]

Radioactive iodine 131 thyroid ablation has been used as an alternative to surgical excision of a symptomatic gland. It has been found to result in unpredictable thyroid shrinkage and is reserved for patients who are deemed unfit for surgery or who refuse surgical intervention.[23]

CONCLUSIONS

1. Physical examination, thyroid function tests, and radionuclide scanning are essential in establishing the diagnosis of lingual thyroid. Biopsy is unnecessary and carries the risk of hemorrhage.

2. Suppressive therapy with exogenous thyroid hormone is the mainstay of medical management for the majority of patients.

3. Endoscopic photography is an excellent means of documenting gland size and airway status.

4. Both CT and MRI scans are useful adjuncts in demonstrating airway patency and gland size, and when planning surgical intervention.

5. Total surgical excision of lingual thyroid tissue is preferred for cases of progression of symptoms despite adequate thyroid suppression or in cases of emergent airway compromise or hemorrhage.

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POSTOPERATIVE CARE FOLLOWING SINGLE-STAGE LARYNGOTRACHEOPLASTY

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Single-stage laryngotracheoplasty (SSLTP) provides a method of correcting mild-to-moderate laryngotracheal stenosis while avoiding the risks of prolonged laryngeal stenting. Pediatric patients are orally intubated for 5 to 7 days postoperatively to ensure an adequate airway while edema resolves and healing begins. During this period, continuous neuromuscular blockade has been advocated in infants and young children to avoid endotracheal tube trauma to the fresh graft and potentially life-threatening accidental decannulation. Pulmonary atelectasis is the most common morbidity associated with prolonged neuromuscular blockade. Neuromuscular weakness also may follow prolonged paralysis and prolong hospitalization. This paper compares the postoperative course of 17 patients who underwent 18 SSLTP procedures by the senior author. The first 8 patients received continuous neuromuscular blockade in the early postoperative period. To reduce perceived morbidity, the last 9 patients were managed with a protocol that incorporated daily 4- to 8-hour "interruptions" of paralysis. Seven patients tolerated this protocol modification. As a group, these patients had less postoperative pulmonary atelectasis prior to extubation ($p < .05$) and were extubated sooner than patients receiving continuous neuromuscular blockade ($p < .05$) without compromising the surgical success of the procedure. Intermittent paralysis permitted for more accurate assessment of pain control and protected against accidental drug accumulation. Although self-extubation did not occur, diligent nursing care with adequate sedation and analgesia is necessary to avoid the risk of accidental extubation.

KEY WORDS — neuromuscular blocking agents, single-stage laryngotracheoplasty.

INTRODUCTION

The efficacy of single-stage laryngotracheoplasty (SSLTP) in correcting mild-to-moderate laryngotracheal stenosis is well recognized.[1-4] Surgical expansion of the airway followed by a short period of endotracheal intubation obviates the need for prolonged laryngeal stenting with its associated risks of granulation tissue formation, restenosis, and death from airway obstruction. Single-stage laryngotracheoplasty was first described by Prescott[1] in South Africa in 1988 following the successful decannulation of 5 tracheotomy-dependent children with subglottic stenosis. The procedure gained popularity in the United States in 1991, when decannulation was reported by Lusk et al[2] in 17 of 19 pediatric and adult patients and by Seid et al[3] in 12 of 13 pediatric patients.

The success of SSLTP is dependent not only on surgical technique, but also on postoperative management. To prevent graft trauma and accidental life-threatening extubation, pediatric patients usually are immobilized. While other children are controlled well with sedation and analgesia, infants and younger children often require pharmacologic paralysis by neuromuscular blockade.[3] Careful attention to pulmonary toilet is necessary to minimize the associated pulmonary morbidity of prolonged paralysis.

The senior author (R.J.H.S.) performed 18 SSLTPs in 17 infants and children over a 2-year period beginning in August 1992. Sixteen patients were decannulated. Despite the success of the surgical procedure, the postoperative pulmonary morbidity and neuromuscular weakness experienced by the first 8 patients were alarming. These children all developed some degree of migratory atelectasis, often with exacerbation of reactive airway disease or pulmonary infiltrates despite intensive pulmonary toilet, bronchodilator therapy, broad-spectrum antibiotics, log rolling, and chest physiotherapy. These complications also have been noted by Seid et al[3] in patients undergoing prolonged continuous neuromuscular blockade.

In an effort to reduce the morbidity of prolonged neuromuscular blockade, for the last 9 patients the postoperative protocol was changed to incorporate daily interruptions from paralysis. This retrospective study compares the early postoperative outcome following SSLTP in these two groups of patients (group 1, with continuous neuromuscular blockade; and group 2, with intermittent neuromuscular blockade).

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Patient outcome is assessed with regard to protocol tolerance, success of decannulation, early postoperative pulmonary morbidity, time to extubation, and duration of hospitalization following extubation.

MATERIALS AND METHODS

Seventeen patients (10 girls) underwent correction of laryngotracheal stenosis or tracheal obstruction. Four patients had isolated subglottic stenosis (Cotton grades I-III), 4 patients had subglottic stenosis (Cotton grades I-III) with tracheal stenosis or tracheomalacia, 4 patients had upper tracheal stenosis and/or tracheomalacia, 1 patient had lower tracheal stenosis and tracheomalacia, 1 patient had a supraglottic web, 2 patients had glottic webs with subglottic stenosis (Cotton grades I-III), and 1 patient had a lower tracheal duplication cyst. Four patients failed attempts at laryngotracheal reconstruction at outside institutions prior to referral. Twelve patients were tracheotomy-dependent and 2 were orally intubated at the time of the procedure. Follow-up ranged from 12 to 30 months.

Laryngotracheal reconstruction was performed as previously described with insertion of a cartilage graft.[5] Anterior cricoid split procedures were not included in the analysis. Costal grafts were placed in the anterior larynx and/or upper trachea in 13 cases, in the anterior and posterior larynx in 2 cases, and in the anterior lower trachea in 2 cases. Lateral tracheal costal cartilage battens also were placed for moderate-to-severe tracheomalacia in 3 patients. Patients were orally intubated with an appropriate-size endotracheal tube and transferred to the pediatric or neonatal intensive care unit following surgery. Ventilation parameters were established for each patient based on weight and underlying pulmonary status. Tidal volume, positive end expiratory pressure, pressure support, respiratory rate, and delivered oxygen were adjusted to optimize ventilation. Continuous infusions of benzodiazepines (midazolam maleate or diazepam) and narcotics (morphine sulfate or fentanyl citrate) were administered to all patients. Intravenous neuromuscular blockade was initiated with an intermediate-acting (vecuronium bromide or atracurium besylate) or long-acting (pancuronium bromide) nondepolarizing agent.

All patients received intravenous antireflux medication and broad-spectrum antibiotics, with adjustments in therapy based on the results of intraoperative tracheal cultures. Chest physiotherapy, log rolling, and endotracheal tube suctioning were performed by respiratory therapists every 4 hours, and aerosolized bronchodilators were administered for bronchoconstriction. Bedside supine chest radiographs were obtained each morning. Nutrition was maintained by peripheral or central venous lipid infusion.

Patients were divided into two groups based on their postoperative neuromuscular blockade management. Group 1 patients received continuous postoperative neuromuscular blockade titrated to prevent gross body movement and/or overbreathing of the ventilator. Group 2 patients were intermittently paralyzed and received a minimum of 4- to 8-hour daily holidays from neuromuscular blockade beginning on the first postoperative day. If necessary, sedation was adjusted during this time to allow spontaneous sighs to improve pulmonary function but to prevent purposeful movement predisposing to accidental extubation. Parents were encouraged to remain at the bedside when the neuromuscular blockade infusion was interrupted.

Extubation was planned 48 hours after a peri-endotracheal tube air leak could be auscultated at 20 cm H_2O pressure.[3] Intravenous steroids were initiated, as was diuretic therapy for patients whose weight had increased during the postoperative period. Neuromuscular blockade was discontinued at midnight prior to anticipated extubation, and narcotics and sedatives were weaned as tolerated. Extubation was attempted the following morning if the patient was awake, moving all extremities, and weaned to minimal ventilator settings. Patients who had undergone posterior graft placement were extubated intraoperatively to confirm proper graft position and stability. If the initial extubation was unsuccessful, patients were reintubated with a smaller-diameter endotracheal tube and sedated. Neuromuscular blockade was not resumed in these patients, and extubation was again attempted 24 to 48 hours later.

Following extubation, patients were observed overnight in the intensive care unit and transferred to the pediatric otolaryngology ward the following morning if blood gas results were stable, oxygen requirements were minimal, and signs of respiratory obstruction were absent. Patients were discharged when oral intake returned to baseline. Steroids were discontinued without taper prior to discharge.

At the conclusion of the study, the outcomes of the two groups were compared with respect to tolerance of the protocol, success of decannulation, pulmonary morbidity, time until extubation, and number of days between extubation and hospital discharge. The last two parameters were compared by an unpaired *t*-test. Pulmonary morbidity from prolonged intubation and neuromuscular blockade was assessed by examination of daily chest radiographs. One pediatric radiologist, blinded to the patients' group assignment to avoid bias, graded the degree of atelectasis or infil-

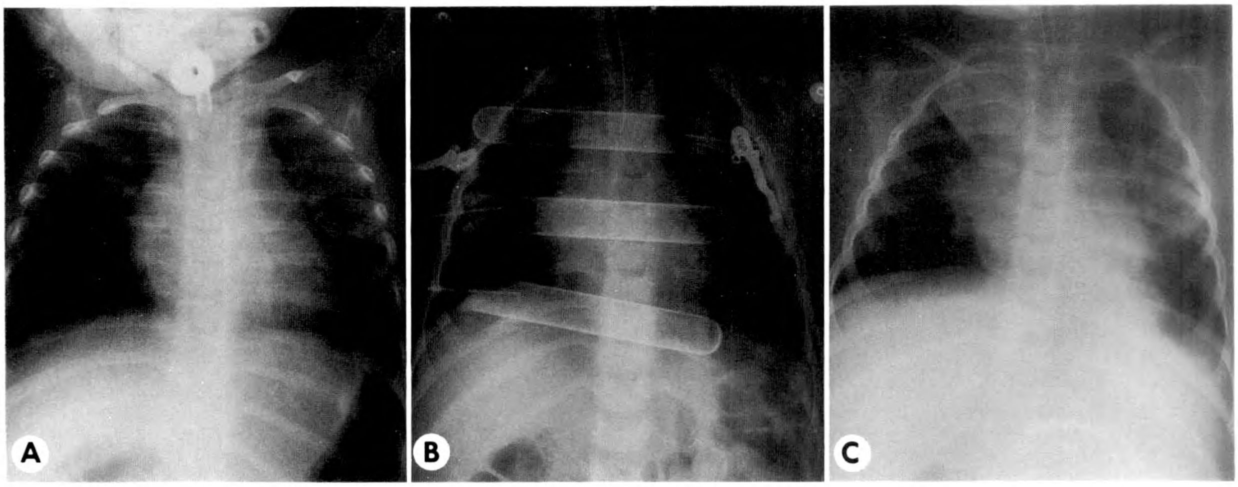

Fig 1. Chest radiographs demonstrating postoperative progression of atelectasis while patients were receiving continuous neuromuscular blockade. A) Preoperative film with no atelectasis or infiltrate (score 0.00). B) Immediate postoperative film with right upper lobe atelectasis and infiltrate (score 2.00). C) Postoperative day 3 film with right upper and left lower lobe atelectasis and infiltrate (score 4.00).

trate on a scale from 0.00 to 5.00, with greater numbers indicating more severe pulmonary compromise (Fig 1; 0.00 for normal findings, 1.00 for minimal streaky involvement, 2.00 for less than one lobe involvement, 3.00 for one lobe involvement, 4.00 for more than one lobe involvement, and 5.00 for total collapse of lung). The change in mean radiographic scores between films taken in the immediate postoperative period versus films taken the day prior to extubation was compared for the two groups by a repeated measures analysis of variance. The mean difference between scores was compared between groups 1 and 2 by a *t*-test. Because pulmonary morbidity is strongly influenced by the duration of intubation, subsets of 7 patients in each group who were decannulated between 5 and 8 days also were compared.

RESULTS

Tolerance of Protocol. Seventeen patients underwent 18 SSLTPs. Eight patients were continuously paralyzed during their postoperative course and were placed in group 1. Seven of 9 patients tolerated intermittent neuromuscular blockade (78%) and form group 2 ($n = 7$). Two patients became too agitated when paralysis was interrupted and neuromuscular blockade was resumed. One of these patients was paralyzed continuously, and her postoperative course is assessed with that of group 1 patients ($n = 9$). The other patient received half her dose of neuromuscular blockade for the duration of her "holiday." Her postoperative paralysis schedule was dissimilar to that used for group 1 and group 2 patients, and she was not included in the comparisons.

Success of Decannulation. Decannulation was equally successful between group 1 and group 2 patients ($p > .05$). Eight of 9 group 1 patients (89%) were decannulated. The failed procedure occurred in a patient with coexisting bronchopulmonary dysplasia, and a tracheotomy ultimately was required for inadequate pulmonary reserve and ventilator dependency. In group 2, all 7 patients were decannulated, although 1 patient developed an infected neck wound 3 days after the first successful extubation and required a second SSLTP to replace a partially dehiscent graft and prevent mediastinitis. Following another 6 days of interrupted paralysis, she was again extubated without further complication. Both of her postoperative courses adhered to the group 2 protocol and were assessed independently with regard to pulmonary morbidity and time to extubation. The ultimate success of decannulation in all patients was 94%.

Pulmonary Morbidity. All patients except 1 child in group 2 demonstrated some degree of atelectasis postoperatively. In the immediate postoperative period, mean atelectasis scores were similar between groups ($p > .90$, Fig 2). However, while the mean atelectasis score increased significantly by the day prior to extubation for group 1 patients ($p = .01$), it remained unchanged for group 2 patients ($p > .50$). The mean score on the day prior to extubation also was significantly greater for group 1 patients compared to group 2 patients ($p < .01$). Atelectasis is more common with bronchopulmonary dysplasia, and each group had 2 children with this diagnosis.

Subsets of 7 patients in each group extubated between 5 and 8 days also were analyzed to eliminate duration of intubation as a factor in the atelectasis score. The excluded patients included 2 children in group 1 who were extubated on postoperative day 10

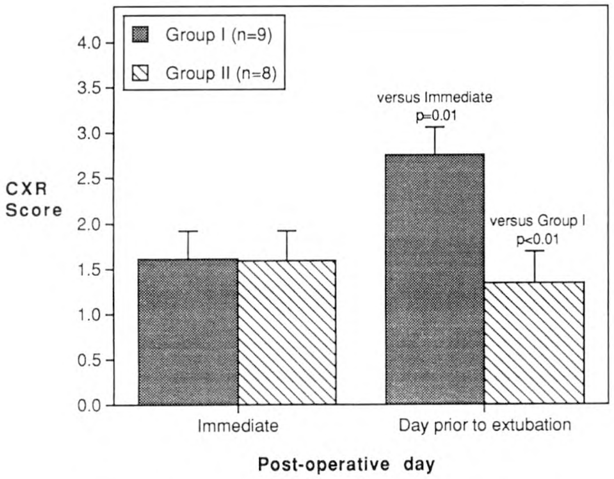

Fig 2. Mean difference between immediate postoperative radiographic scores (left) and day prior to extubation scores (right) between group 1 and group 2 patients. Immediate postoperative scores were similar between two groups. Mean group 1 score increased significantly when compared to immediate postoperative group 1 score ($p = .01$) and pre-extubation group 2 score ($p < .01$).

and 1 child in group 2 who was extubated on postoperative day 3. On the day prior to extubation, comparison of these subsets showed that group 1 patients still developed more atelectasis than group 2 patients ($p < .05$).

Duration of Intubation. Group 2 patients were extubated sooner (mean 5.6 days) than group 1 patients (mean 8.8 days, $p < .05$). Three group 1 patients without underlying neuromuscular problems failed extubation because of respiratory fatigue and/or atelectasis that caused severe hypoxemia and necessitated reintubation. The average atelectasis score on the day of attempted extubation for these patients was 2.8. Although all 3 were later extubated, their initial failures contributed markedly to the significant differences in duration of intubation between the two groups.

Accidental Decannulation. The group 1 infant who failed decannulation remained intubated and mechanically ventilated because of severe bronchopulmonary dysplasia. All neuromuscular blockade was discontinued by the pediatric intensivists on day 5 because of severe and progressive atelectasis. The patient self-extubated 5 days later and required an emergent tracheotomy through his graft site, illustrating the risk of accidental self-extubation when no paralysis is utilized. No group 2 patient self-extubated.

Narcotic Withdrawal. Symptoms of narcotic withdrawal were noted in 2 patients in each group. Manifestations of anxiety, visual hallucinations, and tremors resolved after morphine sulfate was resumed and slowly tapered.

DISCUSSION

The success of SSLTP is dependent not only on surgical technique but also on careful postoperative management. Endotracheal intubation during the first postoperative week is recommended to prevent obstruction from early postoperative edema and to allow wound healing to occur. In older, cooperative children, intravenous sedation and analgesia suffice during the intubation period, but in younger children, neuromuscular blockade is typically instituted. Continuous neuromuscular blockade and positive pressure ventilation predispose to retention of secretions and subsequent atelectasis in 48% to 100% of patients undergoing prolonged intubation after an SSLTP or an anterior cricoid split procedure.[3,4,6,7] The benefits of intermittent paralysis for patients undergoing SSLTP have not been previously explored.

In this study, we found that the degree of atelectasis was less in patients who had daily interruptions from neuromuscular blockade. Although patients in both study groups had similar atelectasis scores on their immediate postoperative chest radiographs, by the day prior to extubation, atelectasis had increased in group 1 patients and was significantly greater than that in group 2 patients. We attribute this difference to the lack of daily holidays from neuromuscular blockade, as other contributing factors such as bronchodilator therapy, chest physical therapy, endotracheal tube suctioning, and mechanical ventilation remained similar between groups.

The increased atelectasis of group 1 patients may have contributed to their increased mean duration of intubation compared to group 2 patients. Three group 1 infants failed initial extubation because of poor oxygenation from atelectasis and/or respiratory fatigue. Despite patent reconstructed airways verified by the presence of a peri–endotracheal tube air leak, they could not be successfully extubated until their pulmonary function improved. The additional required intubations neither caused graft trauma nor compromised the eventual success of the surgical procedure. Postoperative SSLTP patients were not transferred from the intensive care unit to the pediatric ward until the morning after extubation. The increased duration of intubation of group 1 patients consequently necessitated a longer stay in the intensive care unit. Although cost analysis was not the subject of this manuscript, it would provide an interesting comparison between the forms of care provided to group 1 and 2 patients.

Intermittent paralysis did not affect the ultimate success of extubation, which approached 90% in both groups. The SSLTP failures were not related to the schedule of neuromuscular blockade (one failure occurred in a child with severe bronchopulmonary dysplasia, and a revision procedure was required in a child with a wound infection). The ultimate success of SSLTP was approximately 94%.

While interruption of neuromuscular blockade reduced pulmonary atelectasis and duration of intubation, these benefits must outweigh the risk of accidental extubation, which may be accompanied by devastating side effects, as exemplified by a case of hypoxia-induced cortical blindness in a nonparalyzed child.[8] Although some authors believe that postoperative neuromuscular blockade is not required in pediatric patients, we feel that it provides some assurance against self-extubation events.

In this study, the only self-extubation was by a group 1 patient in whom neuromuscular blockade was stopped because of severe migratory atelectasis. Although our study population was small, incorporating daily interruptions from paralysis in the protocol was not associated with any episodes of self-extubation. However, not all patients were able to tolerate an intermittent paralysis protocol. Two children (22%) initially assigned to group 2 became too agitated when paralysis was withdrawn, and neuromuscular blockade was resumed to avoid self-extubation (at a full paralytic dose in 1 patient and a reduced dose in the other). Vigilant nursing attention also is required to ensure adequate sedation during the 4- to 8-hour period of interruption from paralysis. We advocate scheduling the interruption during the daytime shift, when maximum nursing help is available and parents are more likely to be in attendance.

No significant differences existed between groups 1 and 2 in the duration of postextubation hospitalization. Patients were discharged to home when they demonstrated adequate pulmonary function and nutritional intake, sometimes dependent on previously placed gastrostomy tubes. All patients demonstrated some degree of weakness and many took several days, or in the case of 2 group 1 patients, 1 to 2 weeks, to return to preoperative ambulatory skills. This finding is consistent with our experience with prolonged paralysis (21 days) for complete tracheal reconstruction. Following extubation, these patients may be unable to ambulate for several weeks and may require physical therapy after hospital discharge.

No patient experienced the rare phenomenon of prolonged paralysis following neuromuscular blockade.[9,10] Although myopathy from extended use of neuromuscular blocking agents occurs less commonly in pediatric patients than in adult patients, caution must be taken when administering concomitant medications. Many antibiotics, including aminoglycosides, polypeptides, tetracyclines, and clindamycin, have been implicated in cases of prolonged paralysis.[9,11] The penicillin and cephalosporin families have not been reported to cause prolonged paralysis, and a combination of ticarcillin and clavulanic acid is our empiric antibiotic of choice until results of intraoperative cultures are available.

Peri-extubation steroids also must be administered with caution, as they may delay the metabolism of some neuromuscular blocking agents such as vecuronium, an aminosteroid.[3,12,13] Vecuronium was the neuromuscular blocking agent used in 70% of our patients, as it is an intermediate-acting relaxant with negligible histamine release and negligible cardiovascular effects.[14] Many other commonly used neuromuscular blocking agents, such as atracurium, cause histamine release that can exacerbate reactive airway disease.

Adequate sedation and analgesia are paramount to the postoperative SSLTP care of pediatric patients, as signs of pain may be masked by neuromuscular blockade. Tachycardia and salivation suggest discomfort and warrant analgesia. Signs of agitation or pain are recognized more easily during the interruptions from neuromuscular blocking agents — an additional advantage of intermittent paralysis. Although sedative demands increase during the interruption from paralysis, withdrawal symptoms did not occur more frequently in group 2 patients. This suggests that if paralysis is avoided completely, the risk of withdrawal symptoms may be increased, because sedative demands will be greater. Withdrawal symptoms also are more likely if sedatives and narcotics are stopped abruptly, as often happens when patients are transferred from the intensive care unit to the pediatric ward. By slowly tapering the sedative dose, withdrawal symptoms are avoided.

CONCLUSION

Although the success of SSLTP is well recognized, the early postoperative management of these patients is not standardized and is poorly described. Postoperative intubation in older children is usually well tolerated with sedation and analgesia alone. Younger children require high doses of sedatives and narcotics to safely tolerate intubation, and we prefer to manage their early postoperative course with neuromuscular blockade. Prolonged continuous neuromuscular blockade induces pulmonary atelectasis and neuromuscular weakness. We have demonstrated that by interrupting paralysis for 4 to 8 hours each day, the degree of atelectasis is significantly reduced. The risk of accidental extubation was not increased; this finding suggests that with vigilant nursing care, self-extubation events can be minimized.

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MIDDLE EAR RECONSTRUCTION BY TYMPANO-OSSICULAR ALLOGRAFTS

The Third International Antwerp Course on Middle Ear Reconstruction by Tympano-ossicular Allografts will be held (in English) on May 20-21, 1996, in Antwerp, Belgium. For further information, contact Prof Dr P. Van de Heyning, ENT Secretariat Sonja Beckers, University Hospital Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium; telephone **/32/3/821.34.51; fax **/32/3/825.05.36.

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DISTANCE FROM THE LABYRINTHINE PORTION OF THE FACIAL NERVE TO THE BASAL TURN OF THE COCHLEA

TEMPORAL BONE HISTOPATHOLOGIC STUDY

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The middle cranial fossa approach to lesions of the geniculate ganglion and internal auditory canal preserves cochlear function and affords access to the lateral internal auditory canal. The labyrinthine portion of the facial nerve tends to course near the basal turn of the cochlea, just beneath the middle cranial fossa floor, and is usually dissected in this approach. To determine the distance from the labyrinthine portion of the facial nerve to the basal turn of the cochlea, measurements were obtained in the temporal bones of 24 subjects (48 ears) 9 to 76 years of age. These subjects had no history of facial nerve or ear disease, and had normal audiograms. The distances ranged from 0.06 to 0.80 mm, with 21 of 24 right ears (87.5%) showing distances less than the standard size of the smallest diamond drills (0.6 mm), and 18 of 24 (75%) less than 0.5 mm. Incidental note is made of the distance from the geniculate ganglion to the ampulla of the superior semicircular canal, which ranged from 2.06 to 4.88 mm in the 48 specimens. These measurements can serve as guidelines for the surgeon working in the middle cranial fossa.

KEY WORDS — cochlea, complications, craniotomy, facial nerve, middle cranial fossa, sensorineural hearing loss, temporal bone.

INTRODUCTION

The middle cranial fossa approach to the internal auditory canal and geniculate ganglion preserves hearing while affording access to the entire internal auditory canal, as well as to the labyrinthine, geniculate, and tympanic portions of the facial nerve. One portion of the middle cranial fossa approach involves dissection of the labyrinthine portion of the facial nerve. The course of this portion of the facial nerve is adjacent to the basal turn of the cochlea, just beneath the middle cranial fossa floor, and neurotologists are routinely warned against entering the cochlea in their dissection.[1,2] Temporal bone histopathologic studies of the interrelationships of the facial nerve have failed to focus on this distance from the labyrinthine facial nerve to the basal turn of the cochlea.[3-7] We therefore undertook this study to briefly focus on this particular distance, since avoiding entrance into the cochlea is of major concern in each middle cranial fossa operation. We made incidental note of the distance from the superior semicircular canal ampulla to the geniculate ganglion.

MATERIALS AND METHODS

Twenty-four subjects were selected who ranged from 6 to 76 years in age and who had no history of

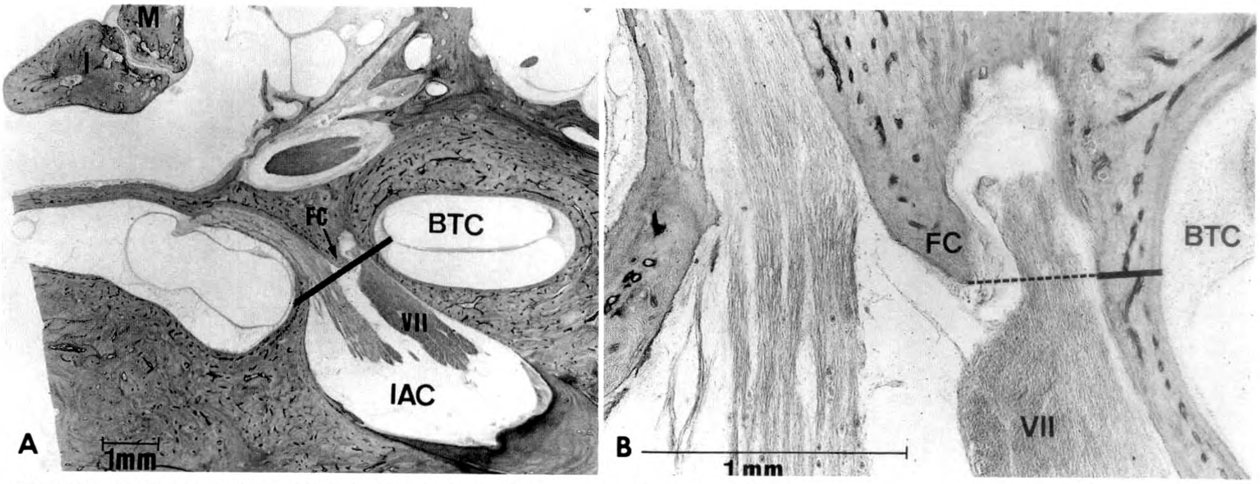

Fig 1. Method of identifying distance from labyrinthine portion of facial nerve (VII) to basal turn of cochlea (BTC; H & E). FC — falciform crest, IAC — internal auditory canal, M — malleus, I — incus. A) Original ×12. B) Original ×65. Solid line — distance measured, dotted line — relation of that distance to FC.

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REPRINTS — Miriam I. Redleaf, MD, Section of Otolaryngology–Head and Neck Surgery, University of Chicago Medical Center, 5841 S Maryland Ave, MC 1035, Chicago, IL 60637.

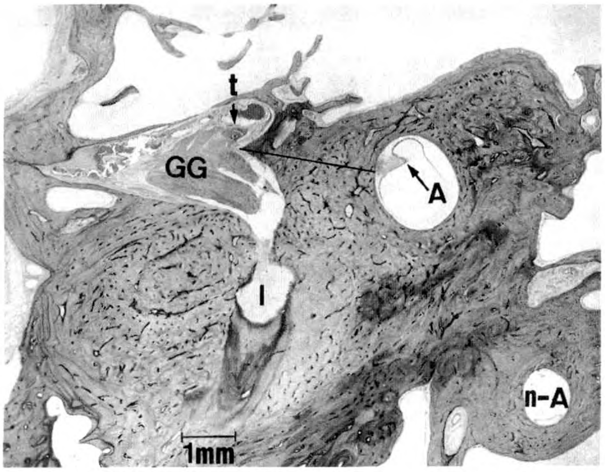

Fig 2. Method of identifying distance from geniculate ganglion (GG) or GG fossa to ampulla of superior semicircular canal (A) (H & E, original ×12). t — tympanic portion of facial nerve, l — labyrinthine portion of facial nerve, n-A — nonampullated end of superior semicircular canal.

facial nerve disease, ear disease, or ear operations. Each had audiometrically documented hearing thresholds that were less than 30 dB at all frequencies tested.

Temporal bones from these individuals had been prepared in the standard fashion consisting of sequential fixation, decalcification, embedding, and sectioning at 20 µm. Every 10th section was stained with hematoxylin and eosin and examined by light microscopy. Selected sections were projected by means of a standard slide projecting lamp and the image was recorded onto opaque paper. An optical micrometer, 2 mm in length and subdivided into 200 µm, was projected onto each image, and its length was also recorded for calibration purposes. Measurements were then made from these projected images, without knowledge of subject number or the lengths measured in the contralateral ear.

For measurement of the distance from the labyrinthine portion of the facial canal to the basal turn of the cochlea, the most inferior section with the falciform crest still evident was selected (Fig 1). The shortest distance across the bony bridge between the labyrinthine facial canal and the basal turn of the cochlea was measured, excluding the membranous periosteum. For measurement of the distance from the ampulla of the superior semicircular canal to the geniculate ganglion, the most superior section with the ampulla and

DISTANCES FROM LABYRINTHINE PORTION OF SEVENTH NERVE TO BASAL TURN OF COCHLEA, AND FROM AMPULLA OF SUPERIOR SEMICIRCULAR CANAL TO GENICULATE GANGLION IN 24 SUBJECTS WITHOUT EAR OR FACIAL NERVE DISEASE

Subject No.	*Sex*	*Age (y)*	*Labyrinthine Portion of Seventh Nerve to Basal Turn (mm)*		*Left-Right Difference (mm)*	*Superior Ampulla to Geniculate (mm)*	
			R	*L*		*R*	*L*
1	M	9	0.80	0.50	0.30	3.50	3.97
2	F	13	0.28	0.25	0.03	2.31	2.41
3	M	16	0.32	0.43	0.11	*	4.52
4	M	20	0.26	0.22	0.04	3.16	2.37
5	M	21	0.29	0.30	0.01	3.50	3.23
6	M	22	0.23	0.26	0.03	4.04	3.27
7	M	23	0.49	0.45	0.04	3.71	*
8	M	26	0.11	0.19	0.08	4.88	3.94
9	M	26	0.70	0.70	0.00	3.98	3.13
10	M	27	0.47	0.25	0.22	3.40	3.19
11	M	27	0.48	0.52	0.04	3.11	3.11
12	M	30	0.40	0.31	0.09	*	3.88
13	M	32	0.69	0.29	0.40	3.61	3.70
14	M	32	0.28	0.18	0.10	2.06	2.11
15	F	39	0.26	0.19	0.07	2.33	2.37
16	M	41	0.43	0.37	0.06	2.83	3.14
17	M	42	0.33	0.30	0.03	2.83	2.65
18	F	42	0.53	0.32	0.21	3.69	3.56
19	F	50	0.45	0.36	0.09	*	3.68
20	M	50	0.23	0.06	0.17	4.45	3.96
21	F	63	0.56	0.64	0.08	2.33	2.58
22	M	68	0.55	0.45	0.10	3.61	3.58
23	M	68	0.36	0.32	0.04	3.81	2.91
24	F	76	0.31	0.43	0.12	3.55	3.86

*No suitable section identified for measurement.

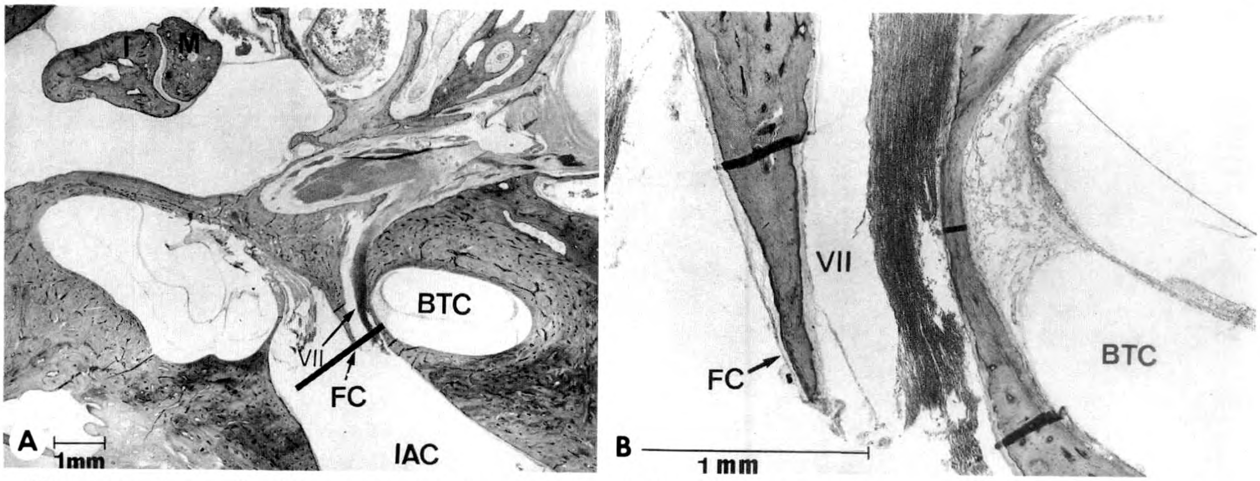

Fig 3. Photomicrographs of distance from labyrinthine portion of left facial nerve (VII) to left basal turn of cochlea (BTC) in patient 20 (H & E). IAC — internal auditory canal, FC — falciform crest, M — malleus, I — incus. This patient had no ear or facial nerve complaints. Distance pictured is 0.06 mm. A) Original ×12. B) Original ×65.

either the geniculate ganglion or the geniculate ganglion fossa was selected (Fig 2). The distance from the semicircular canal to the forking of the tympanic and labyrinthine portions of the facial nerve from the ganglion was measured. Specimens that lacked any of these landmarks were excluded.

RESULTS

Measurements obtained in the 24 subjects are listed in the Table. The range of distances from the labyrinthine portion of the facial nerve to the basal turn of the cochlea was 0.06 to 0.80 mm. These data consisted of 48 pairs of ears from 24 individuals. Therefore, to avoid weighting bias, only the right ear was considered in determining percentages of patients with various distances. Twenty-one of 24 right ears (87.5%) showed distances less than 0.6 mm, which is the diameter of the smallest standard diamond burs. Eighteen of 24 right ears (75.0%) showed distances less than 0.50 mm. The shortest distance, of 0.06 mm, was seen in a 50-year-old man (Fig 3). The measurements obtained of the left- and right-sided distances were within 0.40 mm of each other, and 17 of 24 pairs (70.8%) were within 0.10 mm of each other. Linear regression analysis could identify no evidence of any relationship of distance to age (Fig 4).

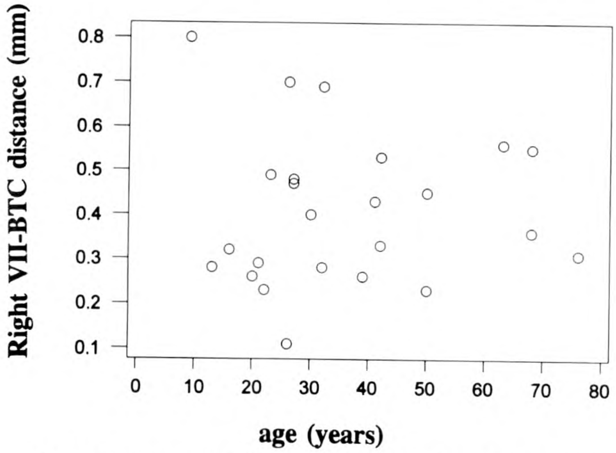

Fig 4. Distance of right labyrinthine portion of seventh cranial nerve (VII) to basal turn of cochlea (BTC) as function of age. No relationship could be demonstrated.

The Table also lists the distances measured from the ampulla of the superior semicircular canal to the geniculate ganglion. Appropriate sections could not be identified in 4 of the 48 ears studied, and no measurements were obtained in these specimens. The distance ranged from 2.06 to 4.88 mm.

DISCUSSION

We have systematically measured the distance from the labyrinthine portion of the facial nerve to the basal turn of the cochlea. Earlier reports warn that the cochlea is "very near,"[1] or that it is 0.5 to 1.0 mm away.[2] We found, however, that the cochlea is often actually much closer to the labyrinthine facial nerve and that in 18 of 24 instances (75%) it was less than 0.5 mm away. When this distance is compared to the size of the smallest diamond drill burs, which are 0.6 mm in diameter, it is evident that extreme care must be exercised during dissection.

The distances from the facial nerve to the cochlea were remarkably symmetric for both ears. The distance from the geniculate ganglion to the ampulla of the superior semicircular canal ranged from about 2 to 5 mm, and averaged about 3 mm. Finally, no relationship could be identified between age and the distance in question.

In summary, this study only makes official what has always been reported anecdotally — that the cochlea is very close to the labyrinthine portion of the facial nerve. The surprising feature here is just how close it is. Several mechanisms of hearing loss after middle cranial fossa surgery have been proposed. These include traction on the cochlear nerve[8,9] and injury to the labyrinthine artery.[9] We wonder if undetected entry into the basal turn might not constitute an additional occult mechanism of hearing loss.

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VESTIBULAR ADAPTATION

The symposium Vestibular Adaptation will be held May 23-25, 1996, in Santa Monica, California. For more information, contact Marjorie Harris, Conference Coordinator, 15-50 Rehabilitation Center, UCLA School of Medicine, Los Angeles, CA 90095-1651; telephone 310-825-5131; fax 310-206-2327.

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LANGUAGE DEVELOPMENT IN COCHLEAR IMPLANTED CHILDREN

The International Conference on Language Development in Cochlear Implanted Children will be held December 8-9, 1996, in Lyon, France. For more information, contact Prof A. H. Morgon, Hopital Edouard Herriot, pavillon U, place d'Arsonval, 69003 Lyon, France; telephone (33) 72.11.05.35; fax (33) 72.11.05.34.

IMAGING CASE STUDY OF THE MONTH

DEVELOPMENT OF A HYPOPLASTIC MAXILLARY SINUS

TODD PROCTOR, MD ROBERT NACLERIO, MD

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INTRODUCTION

The role of surgery in the treatment of pediatric sinusitis remains an area of controversy. Some authors argue that sinusitis in young children should only be treated surgically when complications develop.[1] Others support surgical intervention for medical treatment failures in which anatomic abnormalities impede drainage.[2] The following case report exemplifies through serial computed tomography (CT) a patient who demonstrates a mechanical obstruction that progresses to a hypoplastic maxillary sinus.

CASE REPORT AND RADIOLOGIC FINDINGS

A 2-year-old boy presented with chronic purulent nasal drainage and nasal blockage. On February 3, 1992, CT showed bilateral opacification of the maxillary antra compatible with pansinusitis (Fig 1A). The patient underwent antibiotic therapy and the CT scan was repeated on March 30, 1992 (Fig 1B). The right nasal sinuses had improved; however, significant disease remained on the left side. The mother chose to continue medical management. During the next year, the patient required multiple courses of antibiotics and developed infections while on prophylactic antibiotics. On February 17, 1993, CT showed mucosal thickening of the right maxillary sinus and total opacification of the left maxillary sinus (Fig 1C). The left uncinate process appeared atelectatic, whereas the ethmoid sinuses were greatly improved

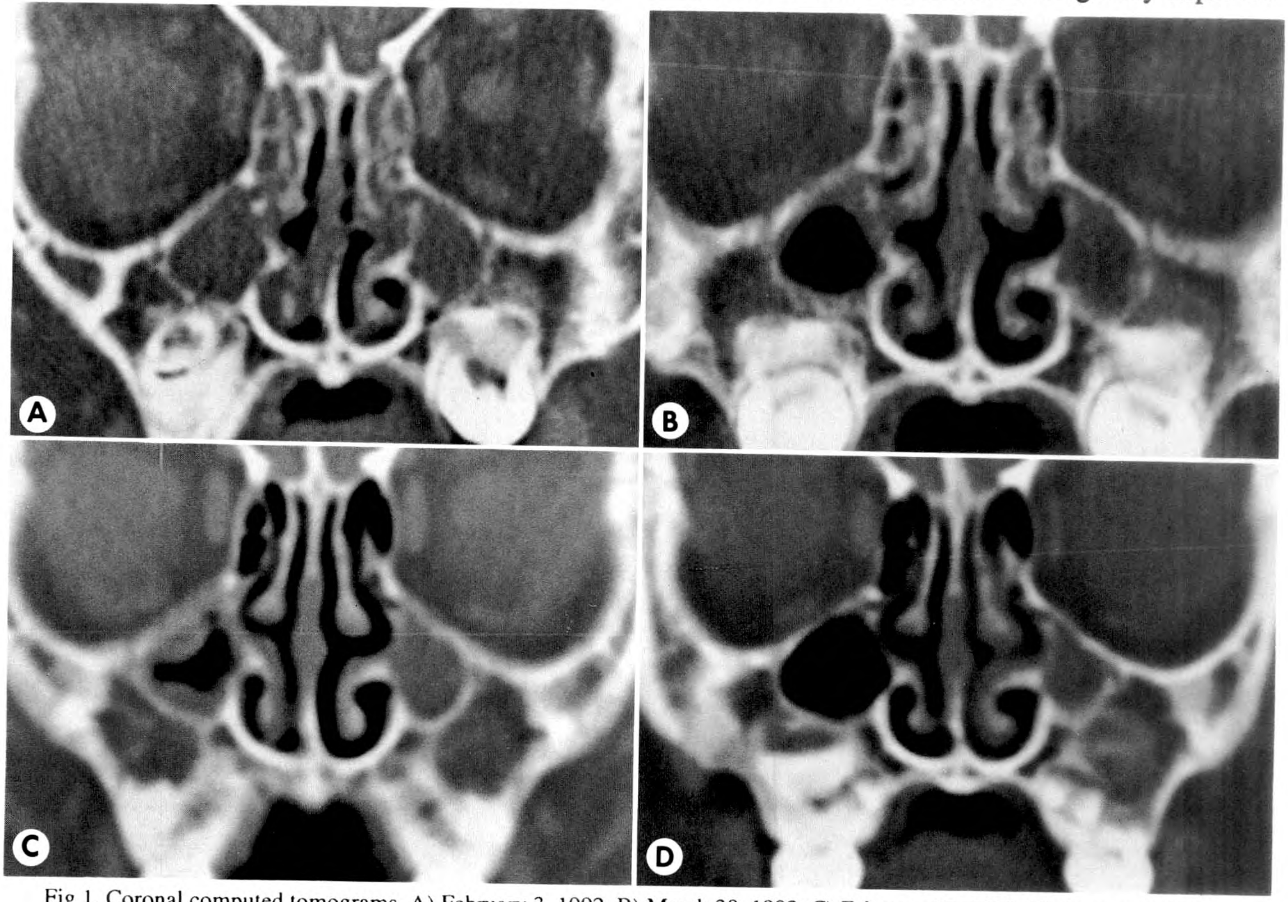

Fig 1. Coronal computed tomograms. A) February 3, 1992. B) March 30, 1992. C) February 17, 1993. D) January 4, 1994.

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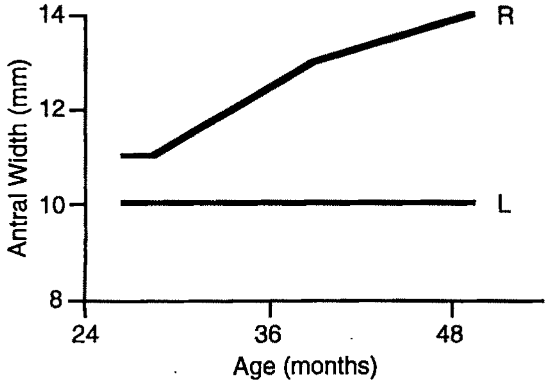

Fig 2. Maximal horizontal antral width on computed tomography by age.

from 1 year earlier. The mother again opted for medical treatment. The child was referred 1 year later with persistent symptoms. Immunologic and allergy workups, including a sweat test for cystic fibrosis, were repeatedly negative. Attempts at office endoscopy were unsuccessful. A CT scan performed January 4, 1994 (Fig 1D), showed complete opacification of the left maxillary sinus, while all other sinuses were clear. The left maxillary sinus was hypoplastic and the uncinate process was clearly atelectatic. Because of the repeated failures of medical treatment and the presence of a defined anatomic abnormality in the absence of an underlying systemic disease, the child underwent a left uncinectomy and maxillary antrostomy. He stopped his continuous use of antibiotics and has done well in the 6 months since surgery.

The maximal horizontal antral width was measured from similar coronal images (Fig 1). The results show progressive growth of the right maxillary antrum and the absence of growth on the left (Fig 2).

DISCUSSION

This case illustrates, through serial CT scans, the development of a hypoplastic maxillary sinus and an atelectatic uncinate process in a patient with chronic sinusitis who was treated medically over a 2-year period. It appears from these scans that the uncinate process became atelectatic and blocked the maxillary ostia, preventing drainage. This process provided a milieu for further infections that inhibited sinus growth.

Although a hypoplastic maxillary sinus is associated with chronic sinusitis (the incidence is approximately 1%), it is unique to capture its progression on CT. These findings support the role of surgery in refractory cases of chronic sinusitis in children with anatomic abnormalities. Whether early correction of this abnormality would have prevented the development of the hypoplastic sinus is unknown. Likewise, whether correction of the anatomic abnormality will lead to future growth of the sinus is unknown.

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OTOLARYNGOLOGY UPDATE

The University of California Otolaryngology Update 1996 will be held in San Francisco, California, November 7-10, 1996. For more information, please contact University of California, Office of Continuing Medical Education, 1855 Folsom St, MCB-630, Box 0742, San Francisco, CA 94143-0742; telephone (415) 476-4251; fax (415) 476-0318.

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PATHOLOGY CONSULTATION

CYSTIC FIBROSIS AND THE SINONASAL TRACT

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Cystic fibrosis is considered to be one of the most common fatal inherited diseases. Sinonasal manifestations are not outstanding as compared with those in the lower respiratory tract. Panopacification of the paranasal sinuses is, however, almost universal on radiologic examination of patients, although many of these patients do not have sinonasal symptoms. Approximately 10% to 20% of cystic fibrosis patients will eventually require surgical treatment of their sinuses. All treatment, including surgery, is transiently effective; none is curative.

A generalized exocrinopathy, cystic fibrosis is an autosomal recessive disorder with an estimated carrier rate of about 1 in 20 and a US and European incidence of 1 in 1,600 to 2,000 live births.[1] The cystic fibrosis gene has been localized to region q31 of chromosome 7 and is responsible for a deficiency in a transmembrane regulator for the transport of chloride.[2] Besides an increase in chloride and water flux into cells and a consequent extracellular fluid dehydration, there is a thickening of exocrine gland secretions. The pancreas and the respiratory system are the most seriously affected by the secretory changes, and obstruction of the excretory ducts of exocrine glands is the hallmark of cystic fibrosis.

Paranasal sinus involvement in cystic fibrosis is initiated by a block of the sinus ostium with thickened mucus secretions. Normal mucus has two layers: an inner, serous (sol phase) layer and an outer, more viscous (gel phase) layer.[3] Ciliary motion is primarily in the sol phase, with the gel phase transported *over* the sol phase when the tips of the cilia touch the outer layer during the ciliary beat. Normal mucociliary clearance is dependent on a proper balance between the two phases.[3]

An exaggerated form of imbalance is seen in cystic fibrosis. The sequence of events is as follows: increased viscosity of mucus → slowing of transport to the sinus ostium → retention of mucus and an increase in viscosity and thickness of the mucus → further stasis and more changes in the viscoelastic properties of mucus → plugging of ostium → hypoxia and carbon dioxide retention → ciliary injury, mucosal edema, and inflammation → bacterial colonization. The majority of patients are colonized by at least one organism, notably *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Hemophilus influenzae*.[3,4] Colonization alone does not imply a uniform progress to infection, but when infection occurs, it tends to be severe.[5] It is of interest, however, that complications of sinusitis, eg, osteomyelitis and orbital or cerebral abscesses, are rare.[1,5] This has been considered to be a result of the frequent use of antibiotics and/or prevention of spread by thickened bone secondary to a chronic osteitis.[1] It should be noted that the paranasal sinuses are not a reservoir for a descending infection of the lungs.

A great majority of patients with cystic fibrosis develop disease of their sinuses at some time during their lives. Almost all patients older than 8 months have panopacification of their paranasal sinuses (with the exception of the frontal sinus, which rarely develops in cystic fibrosis patients).[1,3,5]

Clinical pansinusitis and nasal polyps usually occur in later childhood or in teenagers. Polyps afflict between 10% and 48% of patients but are rare in adults.[1,3,5] If a child has *bilateral* nasal polyps before the age of 10 years, the possibility of cystic fibrosis should be considered as a basis.[1,3,5]

Can sinonasal polyps from patients with cystic fibrosis be distinguished from atopic nasal polyps? Probably not. The polyps seen in cystic fibrosis are inflammatory in nature and might arise from either an infectious or allergic cause. Tos et al[6] studied and compared 11 cystic fibrosis polyps to 102 non–cystic fibrosis polyps and found no difference in density, distribution, or architecture of glands between the two types of polyps. They also indicated that there were no histologic differences in the surface epithelium or the stroma. Oppenheimer and Rosenstein,[7] using simple differential stains, concluded that there were three histologic changes that indicated an association with cystic fibrosis: 1) a delicate, barely visible basement membrane of the surface epithelium without submucosal hyalinization, 2) a paucity of

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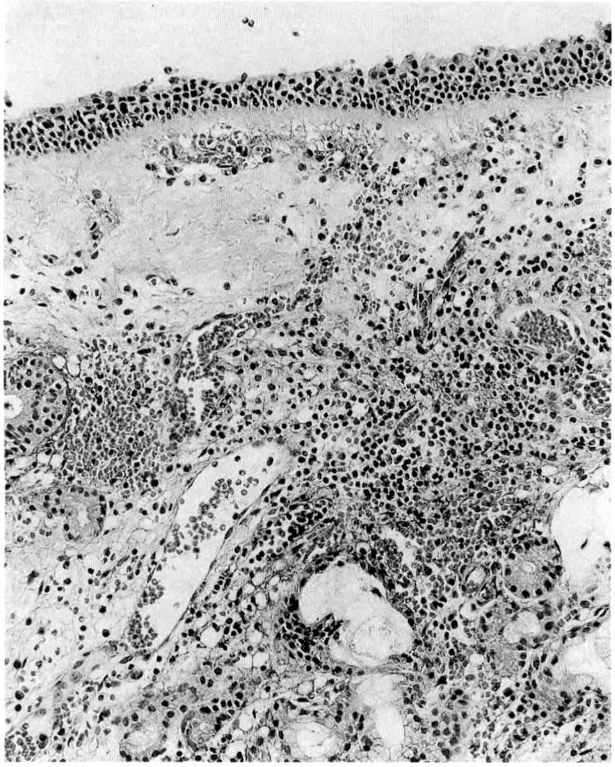

Inflammatory polyp from patient without cystic fibrosis (H & E, original ×80). Note thickened and hyalinized basement membrane.

eosinophils, and 3) a preponderance of *acid* mucin in glands and ducts of the polyps and the surface mucous blanket (Alcian blue–periodic acid–Schiff stains). Polyps from atopic patients were characterized by an extensive thickening of the epithelial basement membrane and its extension into the underlying tissue as an irregular hyalinization (see Figure), a high stromal eosinophil count, and a preponderantly neutral mucin in the glands, cysts, and mucous blanket. Hyperplastic mucous glands, mucous cysts, focal metaplasia of surface epithelia, and an acid mucin in goblet cells were not distinguishing features. The observations by Oppenheimer and Rosenstein[7] are and remain singular, with the weight of evidence supporting Tos et al.[6]

It is further believed that the polyps in patients with cystic fibrosis are not related to atopic disease.[6] The incidence of allergy among patients with cystic fibrosis is not felt to be higher than in the general population.[6] Approximately 10% to 20% of cystic fibrosis patients will eventually require some form of surgical management of their sinuses.[3] Surgical treatment of patients with cystic fibrosis usually consists of removal of the nasal polyps, often with an adjunctive sinus operation.[8] Cepero et al[9] report that the extent of intranasal surgery for polyposis was found to be inversely proportional to the recurrence rate. With nasal polypectomy alone, the recurrence rate reported by Cepero et al[9] was 69%. Combining polypectomy with a sinus operation such as the Caldwell-Luc procedure, external ethmoidectomy, or endoscopic sinus surgery significantly reduced the recurrence rate.[4,8,9]

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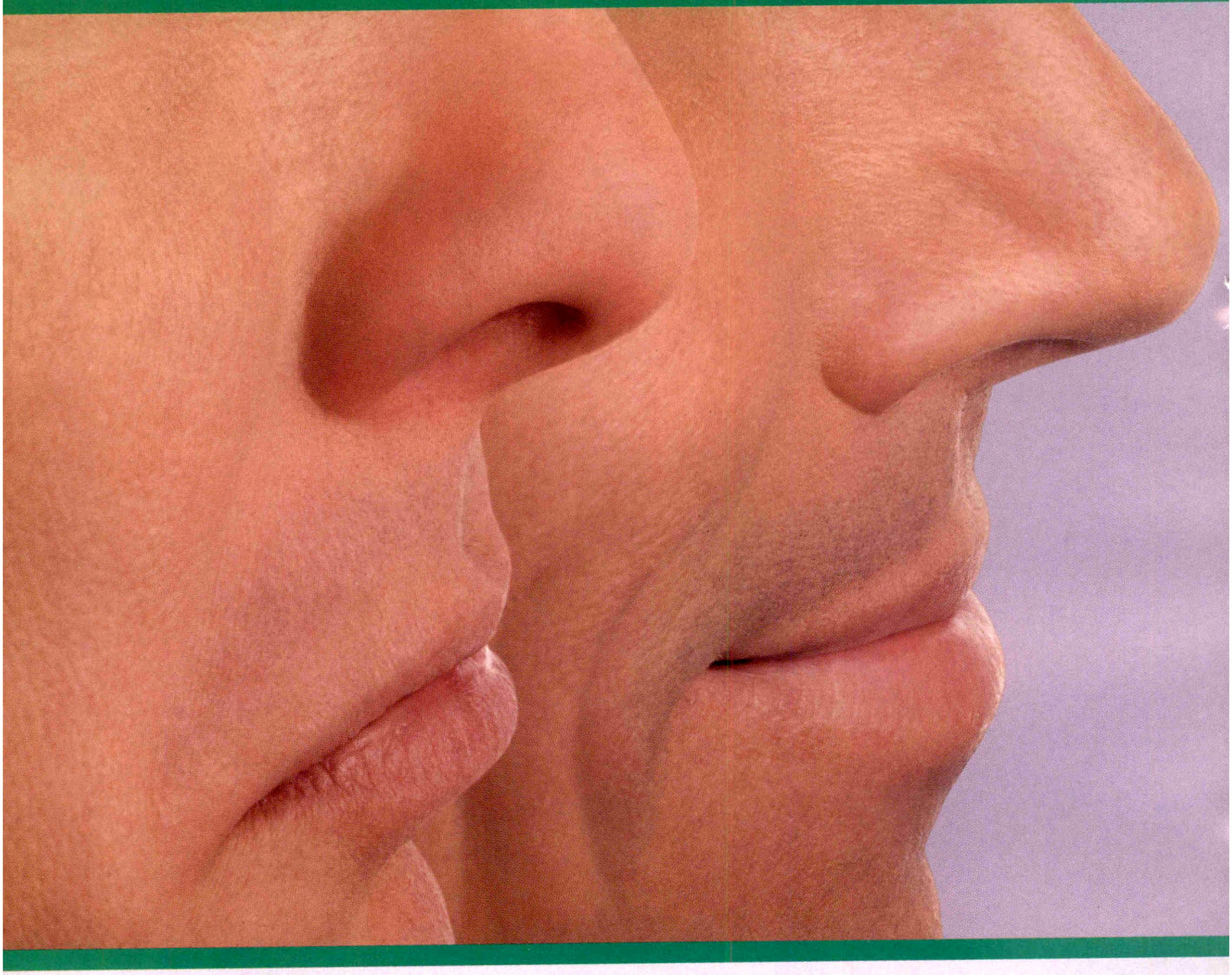

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Seven patients presented to our swallowing center with solid food dysphagia. The age range at presentation was 69 to 90 years. All patients had normal findings on neurologic evaluation, and in those patients undergoing electromyography and nerve conduction studies, results of all such tests were also normal. Pooling of saliva in the pharyngeal recesses was noted on fiberoptic laryngoscopy in most cases. The swallowing videofluoroscopy findings were strikingly similar. All patients had a prominent cricopharyngeus muscle, and some had a prominence in a more proximal portion of the inferior constrictor muscle. All patients had decreased epiglottic tilt and moderate or severe residue in the pharyngeal recesses. Three patients underwent pharyngoesophageal sphincter myotomy. Biopsies of the omohyoid and cricopharyngeus muscles showed inflammatory myopathy with no evidence of inclusion bodies. This is a distinct clinical entity defined by isolated pharyngeal dysphagia in elderly patients with a unique videofluoroscopic appearance and pharyngeal myopathy.

KEY WORDS — cricopharyngeal myotomy, dysphagia, myopathy, swallowing disorders.

INTRODUCTION

Dysphagia is a symptom that can be caused by numerous underlying disorders. The pharyngeal, tongue, and neck muscles are all skeletal muscles; disorders of skeletal muscle could therefore be expected to cause dysphagia if they involve these specific muscle groups. Several skeletal muscle diseases are associated with oropharyngeal dysphagia. These include both muscular dystrophies, such as oculopharyngeal muscular dystrophy, and inflammatory myopathies, such as polymyositis or inclusion body myositis. We present seven patients with oropharyngeal dysphagia caused by an inflammatory myopathy not previously described.

MATERIAL AND METHODS

Patients were referred to the Treatment and Research Center for Swallowing and Motility Disorders at Beth Israel Hospital in Boston, Massachusetts. All of the patients were seen as outpatients by one of the clinicians from the Swallowing Center. The patients were selected for this report because of their strikingly similar and unique videofluoroscopic swallowing findings and similar symptoms.

Physical Examination. Five patients underwent oropharyngeal and flexible fiberoptic pharyngolaryngeal examination by an otolaryngologist (J.S.). Tongue strength was tested by having the patient push the buccal mucosa out against the examiner's external resistance. Tongue coordination was tested by rapid side-to-side tongue motions. Palatal elevation was observed when the patient voiced "ah" and "k." Sensation to light touch was tested by stimulating the posterior pharyngeal wall with the wooden end of a cotton-tipped applicator and asking the patient to lateralize the stimulus.

Videofluoroscopy. Every patient had an oropharyngeal videofluoroscopic swallowing examination. Patients were upright; the oropharynx was viewed in the lateral and anterior-posterior projections. Liquid barium was given by teaspoon in 2-mL and 5-mL volumes, by syringe as a 10-mL bolus, and self-administered by cups in unmeasured volumes. Barium paste was given by teaspoon as a 5-cm^3 bolus. Solid boluses were given as half of a cookie coated with barium paste.

Cricopharyngeal Myotomy. Three patients underwent cricopharyngeal myotomy. After orotracheal intubation, a No. 8 cuffed endotracheal tube was placed in the esophagus under direct vision by means of a sliding laryngoscope. A left transverse neck incision was used to expose the omohyoid muscle, which was transected after a muscle biopsy clamp was applied. The muscle specimen in the clamp was

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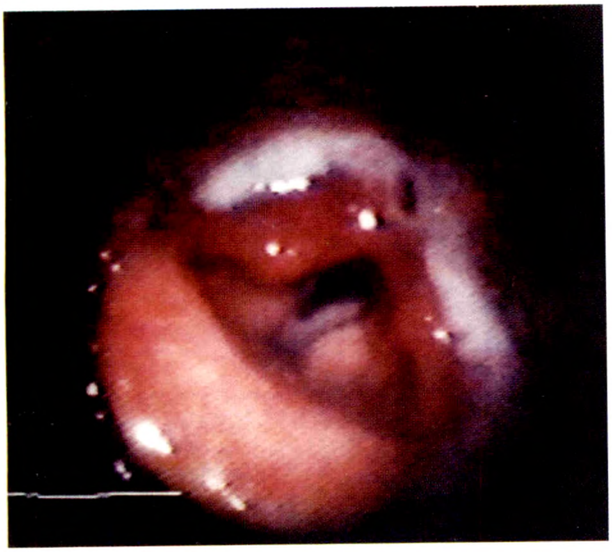

Fig 1. Fiberoptic laryngoscopy showing pooling of secretions in pyriform sinuses and postcricoid area.

wrapped in saline-moistened gauze and sent for histologic examination. The carotid sheath was retracted laterally. The larynx was retracted medially and the pharyngeal constrictor muscles were exposed. The cricopharyngeus (CP) muscle was identified by palpating the cricoid cartilage and visualizing the inserting muscles. Inflating the intraesophageal balloon was helpful in delineating the CP muscle. There was rarely a distinct border between the CP muscle and the inferior constrictor muscle. A myotomy was performed by developing a plane between the pharyngeal mucosa and the constrictor muscles. A 4-cm myotomy was performed with the center at the CP muscle, cephalad extension into the inferior constrictor muscle, and caudal extension into the upper esophageal muscle. The cut ends of the CP muscle were resected and sent in saline-moistened gauze for histologic examination. The esophageal endotracheal tube was removed, a closed suction drain was placed, and the platysma muscle and skin were reapproximated.

Pathologic Studies. Paraffin-embedded material of skeletal muscle was processed for both cross and longitudinal sections and stained with hematoxylin and eosin.

Enzyme histochemical reactions (NADH-TR, ATPase at alkaline and acid pHs, modified Gomori trichrome, periodic acid–Schiff with and without diastase, and oil red O) were performed on one patient.

RESULTS

The patients' ages at presentation ranged from 69 to 90 years. There were six women and one man. The duration of symptoms ranged from 1.5 to 10 years; none had a sudden onset. Patients complained of gradually progressive solid food dysphagia, with the bolus perceived as sticking in the cervical region and requiring either multiple swallows or volitional reverse pharyngeal clearance to be removed. This reverse pharyngeal clearance is described subjectively as a cough and seen videofluoroscopically as posterior movement of the tongue and anterior movement of the posterior pharyngeal wall, resulting in cephalad movement of the bolus out of the pharyngeal recesses. All of the patients had altered their diets to accommodate the dysphagia. Most avoided large solid boluses such as steak or chicken, while others were on a pureed diet. Several patients noted significant lifestyle effects such as avoiding dining in public.

VIDEOFLUOROSCOPY FINDINGS

Pt No.	*Decreased Epiglottic Deflection*	*Residue Pharyngeal Recesses*	*Cricopharyngeal Prominence*	*Cephalad Prominence*	*Aspiration*
1	+	+	+	+	−
2	+	+	+	−	−
3	+	+	+	+	+
4	+	+	+	−	+
5	+	+	+	+	−
6	+	+	+	+	+
7	+	+	+	−	−

Two of the patients underwent previous pharyngoesophageal dilations with mild brief (less than 2 months) reduction in symptoms.

Physical Examination. Five of the patients had a full head and neck examination by an otolaryngologist (J.S.). All five patients had normal tongue strength and mobility, palatal elevation, and posterior pharyngeal wall sensation to light touch. All five patients had pooling of secretions in the valleculae and pyriform sinuses, and one patient also had marked pooling of secretions in the postcricoid area that was documented on fiberoptic videolaryngoscopy (Fig 1). Two patients had a slight tremor of the true vocal cords at the onset of phonation; all patients had normal vocal cord mobility.

Videofluoroscopy. All patients had a normal oral phase of the swallow and abnormalities in the pharyngeal phase. The pharyngeal phase abnormalities (see Table) included decreased epiglottic deflection (seven patients), residue in the valleculae and pyriform sinuses (seven patients), marked prominence of the CP muscle (seven patients), and cephalad prominence of a segment of the pharyngeal constrictor muscle (four patients) (Fig 2). Three patients had some aspiration secondary to decreased laryngeal

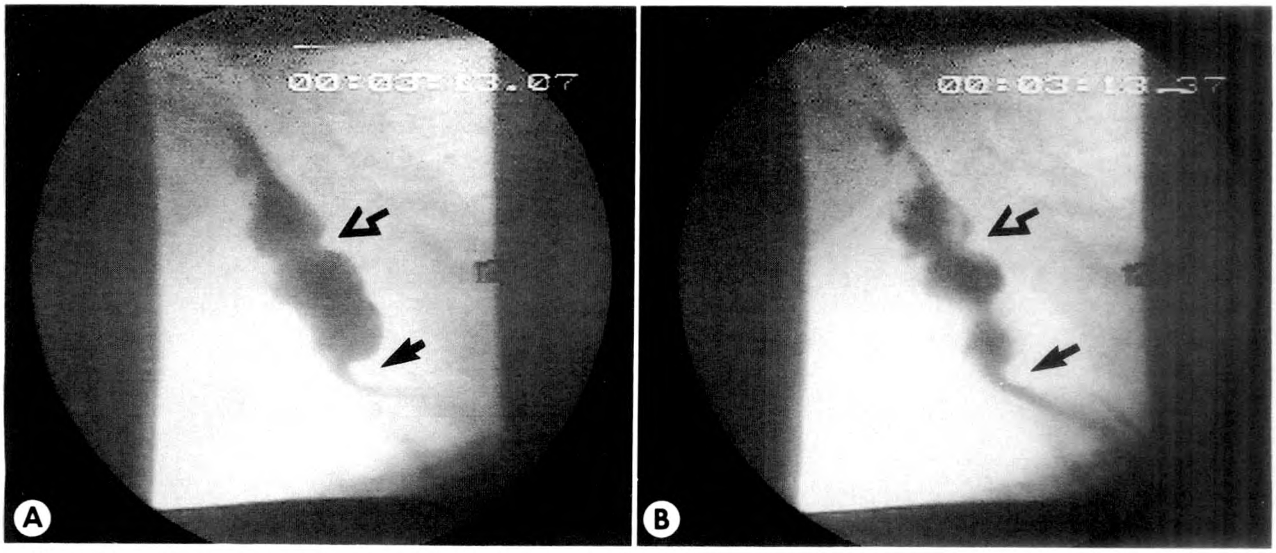

Fig 2. Videofluoroscopy sequence (A, then B) showing persistent marked prominence of cricopharyngeal (CP) muscle (solid arrow) and cephalad prominence of pharyngeal constrictor muscle (open arrow).

elevation.

Neurology Evaluation. Four patients were examined by at least one and sometimes several neurologists. These examinations were all negative, except in one patient, who had a history and physical examination consistent with right temporal limbic and right insular seizures. This patient also had a small right thalamic lacunar abnormality, seen on magnetic resonance imaging, from a "small embolus" in 1981. Three patients had findings on electromyography and nerve conduction studies that were also normal; one of these patients also had electromyographic testing of the thyroarytenoid muscles. Acetylcholine antibody tests were negative in four patients.

Pathology Studies. All three muscle biopsies showed an inflammatory myopathy characterized by 1) multiple foci of interstitial chronic inflammation (lymphocytes, plasma cells, and macrophages), 2) segmental necrosis and myophagocytosis, 3) regenerating muscle fibers (basophilic fibers with large vesicular nuclei and prominent nucleoli), and 4) mild variation in fiber size and focal increase in endomysial connective tissue (Fig 3).

Enzyme histochemical analysis performed on frozen sections on one patient (patient 2) was noncontributory.

Clinical Follow-up. Of the three patients who had a myotomy, one did not note any swallowing improvement, and a follow-up videofluoroscopy showed a persistent, albeit diminished, prominence of the CP muscle. The patient was offered steroid therapy on the basis of inflammatory muscle findings, but she declined. The other two patients noted marked improvement in swallowing function with return to a full diet. In postoperative videofluoroscopy in one patient, there was free passage of the bolus into the esophagus without any prominence of the CP muscle (Fig 4B). This patient has sustained her clinical improvement; she is 9 months postoperative at the time of this writing.

DISCUSSION

During the pharyngeal phase of the swallow, the bolus is propelled through the pharynx from the faucial arches through the pharyngoesophageal segment (PES). This is accomplished by posterior propulsion of the base of the tongue and segmental contraction of the constrictor muscles. The palate makes contact with the posterior pharyngeal wall, thereby closing the nasopharynx. The larynx elevates under the base of the tongue, and the epiglottis tilts posteriorly over the laryngeal vestibule. The PES opens by relaxation of the intrinsic sphincter muscles, the anterior-superior movement of the suprahyoid muscles, and distention of the PES by the bolus. Incomplete opening of the PES can be secondary to a number of factors, including failure of neural inhibition of tonic sphincter contraction, weakness of the suprahyoid musculature, or noncompliance of the intrinsic sphincter muscles.[1] Myopathies affecting the pharyngeal and neck musculature may therefore cause PES dysfunction if they involve the suprahyoid muscles or intrinsic sphincter muscles. But one would also expect some dysfunction of the other aspects of the pharyngeal phase, such as decreased bolus propulsion leading to residue in the valleculae and pyriform sinuses, velopharyngeal weakness causing nasal regurgitation, and decreased laryngeal elevation and epiglottic deflection potentially leading to aspiration.

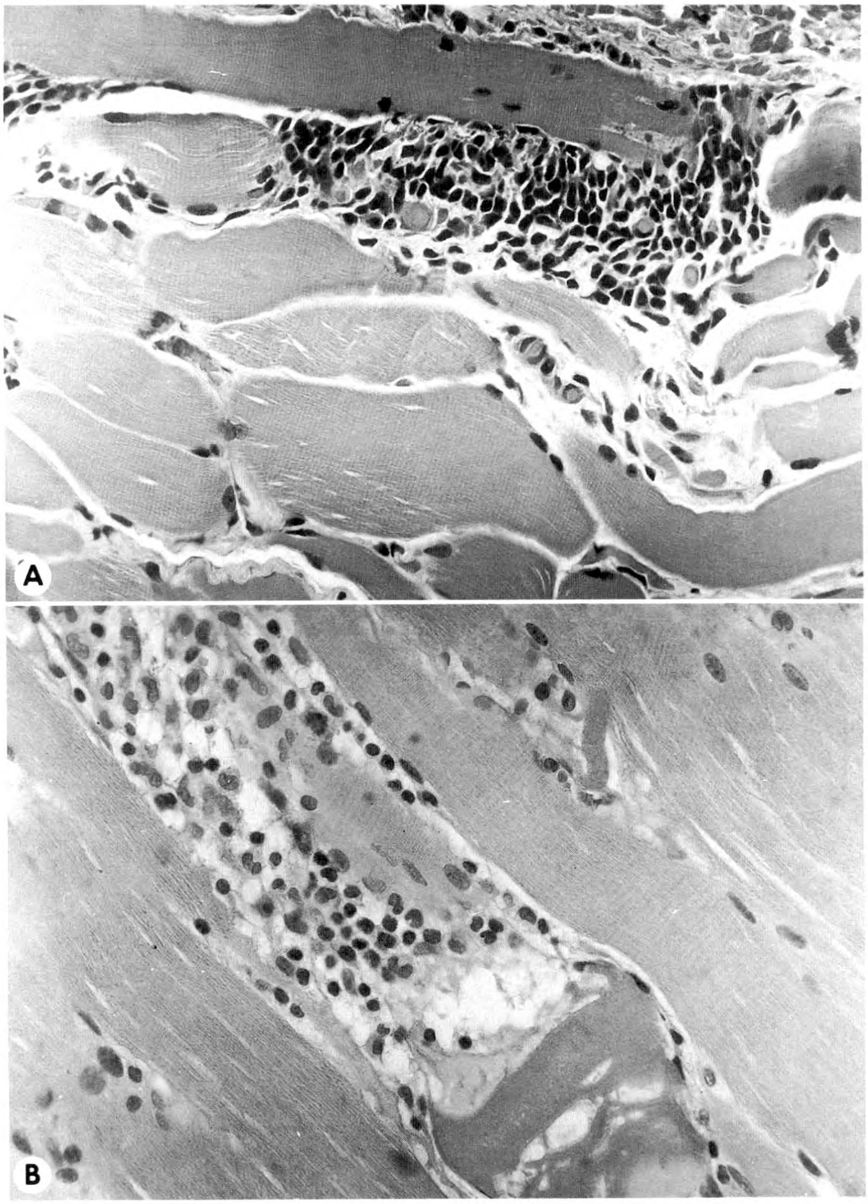

Fig 3. Histology of CP muscle biopsy demonstrating inflammatory myopathy. A) Note interstitial dense chronic cell infiltrate. B) Note myophagocytosis.

There are two categories of myopathies: inflammatory myopathies and muscular dystrophies. Two forms of inflammatory myopathy, polymyositis[2] and inclusion body myositis,[3,4] can both cause dysphagia by involvement of the neck and pharyngeal muscles. Treatment of the polymyositis with steroids will often resolve the dysphagia. Unfortunately, inclusion body myositis is not responsive to steroids, and the efficacy of PES myotomy has not been well studied in these patients.

Oculopharyngeal muscular dystrophy is an inherited autosomal dominant disorder usually affecting patients after age 40. The presenting symptom may be bilateral ptosis or dysphagia. Their videofluoroscopic swallowing studies often show nearly absent laryngeal elevation and epiglottic deflection, massive residue in the pharyngeal recesses or in the entire hypopharynx with no evidence of pharyngeal constrictor function, and a stricturelike appearance of the PES with little bolus passage into the esophagus. There is often nasal regurgitation and aspiration. A diagnosis can be made on a deltoid muscle biopsy, even though the primary muscles affected are the ocular and pharyngeal. These patients do respond to a PES myotomy.[5,6]

Although not as severe a dysfunction as in oculopharyngeal dystrophy, our patients had significant dysphagia causing a major diet change and quality of life issues that prompted them to seek medical attention. The gradual onset is suggestive of a neuromuscular cause rather than a sudden injury from a cerebrovascular accident. Their symptoms reflected problems with bolus propulsion and incomplete opening of the PES. This was documented on both physical

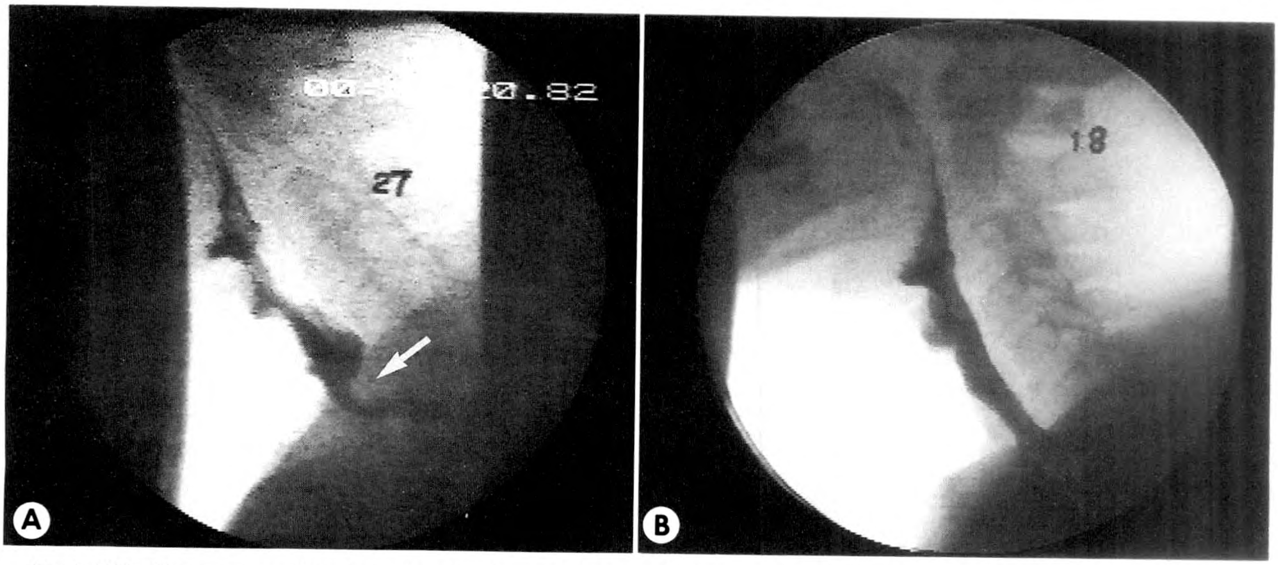

Fig 4. Videofluoroscopy. A) Preoperative, showing prominence of CP muscle (arrow). B) Postoperative, showing free passage of bolus into esophagus with no prominence of CP muscle.

examination and swallowing videofluoroscopy. In no cases were there distal muscles involved or other systemic neuromuscular abnormalities. The patients had swallowing videofluoroscopy findings demonstrating problems with laryngeal elevation, bolus propulsion, and decreased PES opening. These findings are consistent with pharyngeal muscle weakness.

All patients with biopsies had a histologically proven inflammatory myopathy. The presence of the mild variation in fiber size and focal endomysial connective tissue proliferation is difficult to interpret, since there is little knowledge of the normal appearance of these muscles at biopsy.[7,8] Nevertheless, the striking inflammatory and myophagocytic components seen in the biopsies would never be expected in normal muscles.

Two of the three patients responded to a PES myotomy. This response was presumably due to removing a relative outflow obstruction to the weakly propelled bolus. The failure of myotomy in one patient may reflect an incomplete myotomy, although the technique was the same in all three patients.

In theory, an inflammatory myopathy may be responsive to systemic steroid therapy. This may be an alternative to surgery in some patients, but it has its own risks. Also, one would need a muscle biopsy to make the diagnosis. Whether a sternocleidomastoid muscle biopsy under local anesthesia or a more conventional deltoid muscle biopsy would reveal the myopathy in these patients is not yet known.

CONCLUSION

Seven patients with dysphagia were studied. They had symptoms and examinations reflecting poor bolus propulsion and decreased PES opening. Three of the patients underwent a PES myotomy. In two patients the procedure was a therapeutic success, while in one it failed to relieve the dysphagia. All three patients had an inflammatory myopathy of the neck and pharyngeal muscles not previously described.

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LARYNGOTRACHEAL MANIFESTATIONS OF RHINOSCLEROMA

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Rhinoscleroma is a rare, chronic granulomatous disease of infective causation. It usually begins in the nose and may progress to involve the larynx and trachea and cause dysphonia, stridor, and airway obstruction. Early rhinoscleroma is usually successfully treated with oral tetracycline, yet laryngotracheal disease may require operative intervention. The disease is rare in the United States, but with an increase in immigration from endemic areas, otolaryngologists should be familiar with the management of this rare disease. Current literature contains only a few reports describing the manifestations of this disease, mostly in the form of case studies. This study is a retrospective review of our institutional experience with the management of 22 patients with rhinoscleroma, 13 of whom had laryngotracheal involvement. The focus of this report is on the clinical manifestations of laryngotracheal scleroma. All of the patients were treated with long-term antibiotics. Nine patients underwent endoscopy with or without dilation and laser excision. Three patients required emergency tracheostomy, all of whom were ultimately decannulated without any sequelae. A rational approach to management of this unusual disease is provided.

KEY WORDS — granuloma, *Klebsiella rhinoscleromatis*, laryngotracheal scleroma, nose, rhinoscleroma.

INTRODUCTION

Rhinoscleroma (RS) is a rare chronic granulomatous disease caused by *Klebsiella rhinoscleromatis*. It originates in the nose and may progress to involve any part of the respiratory tract.[1] Clinical remission and relapse characterize the disease, making diagnosis and treatment difficult. The disease manifests as four overlapping stages: the catarrhal stage, characterized by prolonged purulent rhinorrhea; the atrophic stage, with mucosal changes and crust formation; the granulomatous stage, characterized by granulomatous nodules in the nose, with or without involvement of other parts of the respiratory tract; and the sclerotic stage, with dense cicatricial fibrosis of the involved tissue.[2] Laryngotracheal manifestations of RS are uncommon, yet potentially life-threatening because of progressive airway obstruction. The reported incidence of laryngotracheal scleroma (LTS) ranges from 15% to 80%.[3,4] In the early stages, LTS may manifest as mild dysphonia, ultimately progressing to airway obstruction and stridor secondary to sclerotic stenosis of the airway.

Endemic in the tropics and subtropics, RS is spread solely in humans under conditions of overcrowding, malnutrition, and poor hygiene.[5] Rhinoscleroma was rarely seen in the United States prior to the late 1960s. The prevalence of RS has increased since then, owing to the influx of immigrants from RS-endemic nations in Central and South America, and the prevalence of US-related medical facilities in the Middle East.[5] Many regions of the United States that do not have large influxes of such immigrants rarely see this disorder. The Mayo Clinic, for example, identified only 6 cases between 1900 and 1991.[6] Because of its rarity, most otolaryngologists have little or no experience with the management of this disease. Very little information exists in the literature on the management of LTS, most of it in the form of a few case reports. The largest series was reported from Egypt in 1989, which discussed the management of postscleroma subglottic stenosis in 6 patients.[7] The current pattern of immigration from endemic areas necessitates vigilance in diagnosis and treatment by the otolaryngologist–head and neck surgeon. An understanding of the approach to LTS and management of its manifestations is essential to the overall management of RS. Over the years, the Los Angeles County–University of Southern California Medical Center (LAC-USC MC) has treated many patients with RS.[8] The present study describes our institution's experience with 22 cases of RS, 13 of which presented with LTS. The focus of this report will be on the laryngotracheal manifestations of RS in our experience with this group of patients. The aim is to provide clinicians with an understanding of the clinical manifestations, diagnosis, and management of LTS.

MATERIALS AND METHODS

The records of 22 patients with biopsy- and culture-positive RS who were treated and followed up by the Department of Otolaryngology–Head and Neck Surgery at the LAC-USC MC between 1982 and 1994 were reviewed. These RS patients under-

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TABLE 1. FINDINGS IN LARYNGOTRACHEAL SCLEROMA PATIENTS

Pt No.	*Age*	*Sex*	*Respiratory Symptoms*	*Laryngeal Findings*	*Tracheal Disease*
1	27	F	Dyspnea on exertion	Granulomas of true and false vocal folds	None
2	30	M	Dyspnea on exertion	Subglottic ulcer	Crusts of anterior wall
3	30	M	Stridor, airway obstruction	Glottic and subglottic stenosis	None
4	37	F	Stridor, airway obstruction	Subglottic stenosis	None
5	34	M	Stridor, airway obstruction	Subglottic stenosis	Tracheal stenosis
6	55	M	Dyspnea on exertion	Glottic stenosis	None
7	40	M	Dyspnea on exertion	Subglottic stenosis	None
8	44	F	Dyspnea on exertion	Subglottic stenosis	None
9	28	F	Dyspnea on exertion	Subglottic stenosis	None
10	26	M	Dyspnea on exertion	Epiglottic and glottic granulomas	None
11	53	M	Dyspnea on exertion	Glottic and subglottic stenosis	None
12	46	F	Dyspnea on exertion	Subglottic stenosis	None
13	22	M	Dyspnea on exertion	Subglottic granulomas	None

went complete head and neck examinations, including indirect laryngoscopy and nasal endoscopy. Serologic workup included complete blood counts, determination of immunoglobulin levels (IgG, IgA, IgM), and protein band electrophoresis. Videolaryngoscopy was performed in patients with rigid and flexible laryngoscopes (Pentax FNL-10RP2 nasopharyngolaryngoscope, Asahi Optical Co, Ltd, Tokyo, Japan). Positive identification of *K rhinoscleromatis* on biopsy and cell culture is diagnostic of the disease, as this organism is not a normal nasal flora. Morphologic similarities between *K rhinoscleromatis* and other *Klebsiella* species, particularly *Klebsiella ozenae*, are well known; therefore, definitive identification of *K rhinoscleromatis* is imperative. The typical histopathologic findings consist of plasma cells, lymphocytes, Russell bodies, and Mikulicz cells containing gram-negative diplobacilli. Immunocytochemistry utilizing antibodies to the O2K3 capsular antigen coupled to a peroxidase-antiperoxidase complex is the single most specific test. This immunoperoxidase test, together with positive histopathologic findings, was used to diagnose RS in the present study.

All 22 patients had involvement of the nasal mucosa: 9 patients in the catarrhal and atrophic stages, 3 in the granulomatous stage, and 10 in the sclerotic stage. Thirteen of the 22 patients had LTS. All of these patients were in the granulomatous and sclerotic stages of their nasal disease. All of the 13 patients presented with dysphonia. Ten of these 13 patients complained of dyspnea on exertion, 3 of whom had severe dyspnea and stridor at rest. Tracheostomy was required in these 3 patients. One of the 3 patients had the tracheostomy performed at an outside hospital 6 months prior to arriving at our institution. Ten patients were initially treated with 40% humidified oxygen via face mask and steroids: intravenous dexamethasone (1 mg/kg per day in divided doses every 6 hours for 72 hours) in 5 patients and oral prednisone (1 mg/kg per day in two divided doses for 2 weeks) in 5 patients. Of the 3 patients who did not receive steroid therapy, in 1 it was because of pregnancy, and in the other 2 it was because of the mild nature of the disease. Direct laryngoscopy and bronchoscopy (DL & B) and biopsies were performed in 9 patients with respiratory symptoms. Dilation of the subglottic stenoses was performed in 3 of these patients, and laser excision of discrete glottic and/or subglottic scleromas was performed in 2 (carbon dioxide laser, Lasersonics Inc, USA).

Intravenous antibiotics (ampicillin sodium 1 g every 6 hours) was instituted in all 22 patients as soon as the diagnosis of RS was clinically suspected. The antibiotics were changed to oral tetracycline (500 mg orally, four times per day) after positive identification of *K rhinoscleromatis* and sensitivity to the antibiotics were determined. All patients were treated with oral antibiotics for 6 months to 2 years until the nasal mucosal biopsies demonstrated no *Klebsiella* organisms. Outpatient follow-up visits ranged from once a week to every other month, depending on the severity of the symptoms. During the follow-up visits, a complete otorhinolaryngology examination and videostroboscopy were performed, and in selected patients, serologic studies of immune markers were performed. Re-biopsy of the nasal scleroma was done after 6 months of antibiotic therapy.

RESULTS

The most common initial laryngotracheal finding was subglottic and/or glottic stenosis, which was present in 9 patients (Table 1 and Fig 1). Granulomas were present in 3 patients, most commonly at the

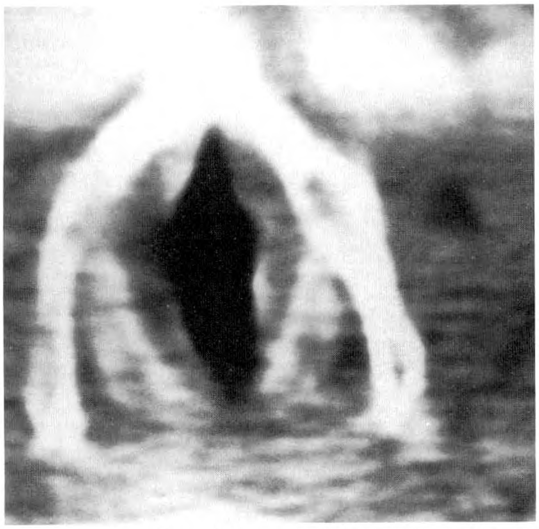

Fig 1. (Patient 5) Axial computed tomogram showing subglottic stenosis due to rhinoscleroma.

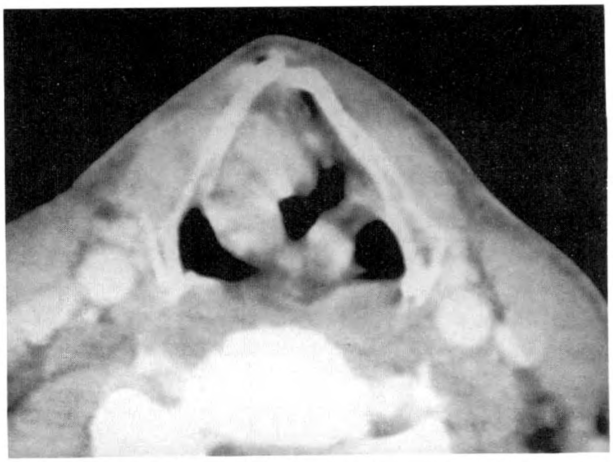

Fig 2. (Patient 3) Axial computed tomogram of larynx showing large exophytic lesion of right glottis and supraglottis with marked narrowing of airway.

glottic level (Fig 2). One patient was noted to have subglottic ulcers. Two patients had tracheal involvement, both limited to the first two tracheal rings.

All 3 patients who underwent tracheostomies were ultimately decannulated. The time interval for decannulation ranged from 6 months to 3 years. Of the remaining 10 patients, 2 were lost to follow-up, 6 patients had improvement of their respiratory symptoms, and in 2 patients the symptoms remained unchanged. None of the patients who had tracheostomies developed distal (lower) tracheal disease (Table 2).

Follow-up laryngeal findings were assessed by outpatient videostroboscopy. The majority of the patients had scarred vocal folds with reduced mobility and/or absence of the mucosal wave. In 2 patients, hyperadduction of the false vocal folds with ventricular phonation was noted. Despite improvement of their nasal or respiratory symptoms, these patients did not demonstrate improvement in vocalization or

TABLE 2. TREATMENT AND OUTCOME OF LARYNGOTRACHEAL SCLEROMA PATIENTS

Pt No.	*Medical Therapy*	*Surgery*	*Outcome of Respiratory Symptoms*
1	Oral tetracycline, nasal spray	None	Unchanged
2	IV ampicillin, oral tetracycline, IV steroids, O2 mist	DL & B	Improved
3	IV ampicillin, oral tetracycline, IV steroids, O2 mist	Tracheostomy, DL & B	Improved, decannulated at 3 y
4	IV ampicillin, oral Keflex,* O2 mist	Tracheostomy, DL & B	Decannulated at 6 mo, lost to follow-up
5	IV ampicillin, oral tetracycline, oral steroids, O2 mist	Tracheostomy, DL & B	Improved, decannulated at 1 y
6	Oral tetracycline, nasal sprays	None	Lost to follow-up
7	IV ampicillin, oral tetracycline, IV steroids, O2 mist	None	Improved
8	Oral tetracycline, nasal sprays, oral steroids	None	Improved
9	IV ampicillin, oral Bactrim, IV steroids, O2 mist	DL & B, dilation, laser excision	Improved
10	IV ampicillin, oral tetracycline, oral steroids, O2 mist	Laser, DL & B	Improved
11	IV ampicillin, oral tetracycline, IV steroids, O2 mist	DL & B, dilation	Unchanged
12	IV ampicillin, oral tetracycline, oral steroids, O2 mist	DL & B	Improved
13	IV ampicillin, oral tetracycline, oral steroids, O2 mist	DL & B, dilation	Lost to follow-up

IV — intravenous, O2 — oxygen, DL & B — direct laryngoscopy and bronchoscopy.

*Patient was pregnant.

vocal fold mobility.

All lesions submitted to biopsy demonstrated *K rhinoscleromatis* on pathologic studies. Grossly, the lesions appeared pale, with diffuse nodular thickening. Microscopically, patients with granulomatous lesions demonstrated submucosal granulomatous infiltrates composed of macrophages with clear to foamy cytoplasm (Mikulicz cells), intimately associated with lymphocytes and plasma cells. In patients with more extensive subglottic disease, thick, irregular connective tissue densities appeared in the submucosa, resulting in cicatricial scarring of the subglottis and glottis. Re-biopsy of the nasal tissue after 6 months of antibiotic therapy demonstrated the presence of fibrotic changes in all patients, without the demonstration of *Klebsiella* organisms.

Serum immune markers demonstrated raised IgA levels (658 mg/100 mL, 536 mg/100 mL, 497 mg/100 mL; normal IgA range, 40 to 400 mg/100 mL) and normal levels of IgG, IgM, proteins, and globulins in 3 patients with early nasal scleroma without LTS. Both patients with discrete laryngotracheal granulomas that were amenable to laser therapy demonstrated raised IgA levels (470 mg/100 mL, 513 mg/100 mL) and normal levels of IgG, IgM, serum proteins, and globulins at the time of surgery, with normalization in IgA levels after 6 months of therapy. One patient with extensive disease who required a tracheostomy demonstrated an IgG level of 2,040 mg/100 mL (normal range, 750 to 1,750 mg/100 mL), a serum protein level of 9.2 g/dL (normal, 6 to 8 g/dL), a beta globulin level of 1.2 g/dL (normal, 0.6 to 1.0 g/dL), and gamma globulin levels of 2.2 g/dL (normal, 0.8 to 1.7 g/dL). These values normalized after 6 months of therapy. One patient with glottic and subglottic stenosis demonstrated decreased CD4 and CD8 levels: CD4 at 451%/mm^3 (normal, 518% to 1,500%/mm^3) and CD8 at 274%/mm^3 (normal, 304% to 970%/mm^3). Follow-up studies demonstrated normalization in these levels in this patient 3 months after completion of therapy.

DISCUSSION

The incidence of laryngotracheal involvement in patients with RS ranges from 15% to 80%.[3,4,8] In our series, the incidence was 59%. In general, patients with LTS have concurrent nasal disease, although isolated laryngotracheal disease without nasal involvement has also been reported.[9]

The subglottic region is the most common site of LTS. It is believed to arise at the junction between the squamous epithelium of the vocal folds and the respiratory epithelium of the subglottic mucosa.[10] Subglottic disease is characterized by chronic scarring with progression to circumferential stenosis (Fig 1). In earlier stages, granulomas may be seen, as observed in 3 of our patients (Fig 2). Downward extension will result in tracheal stenosis. The stages of LTS appear to parallel the stages of the nasal disease, as evidenced in 3 patients with concurrent nasal and laryngeal granulomas and 10 patients with sclerotic disease of both nasal and laryngeal passages. In the early stage of LTS, hoarseness is a common symptom due to vocal fold edema and thickening. Vocal fold erythema and exudates may also occur. Progression to the granulomatous stage is characterized by granulomas affecting the larynx.[6] In our series, it appears that the granulomas occur more commonly in the glottis than in the subglottis. Subglottic granulomas at this stage can cause incomplete adduction on phonation, with weak abduction on inspiration. Ultimately, the disease enters a sclerotic stage in which the granulomas begin to harden with fibrous tissue. Sclerosis of the larynx and trachea leads to circumferential stenosis of the airway, usually at the glottic-subglottic interface, resulting in stridor and airway compromise.

Diagnosis of LTS requires an accurate history, a thorough physical examination, and a high index of suspicion. Laryngeal examination using indirect laryngoscopy with flexible or rigid endoscopes is essential to evaluate the extent of glottic and/or subglottic extension. Computed tomography may be of value in determining the extent of subglottic and tracheal involvement prior to tracheostomy, as the surgeon must place the tracheostomy below the inferior extent of the lesion. Biopsy and bacterial culture are the definitive tests. Microscopic findings are characterized by the presence of Mikulicz cells, Russell bodies, pseudoepitheliomatous hyperplasia, and squamous metaplasia. Immunoperoxidase tests can positively identify the presence of *K rhinoscleromatis* organisms in the tissues. In the presence of positive nasal cultures or pathologic findings on nasal biopsy consistent with RS, and typical findings on indirect laryngeal examination, the presumptive diagnosis of LTS can be made. It is not always essential to have positive laryngeal cultures for the diagnosis of LTS, as DL & B under general anesthesia may not always be possible in all patients. For example, 1 of our patients was pregnant, and DL & B was delayed until after delivery of her baby. In that patient, the diagnosis was made on nasal culture and typical laryngeal findings.

Antibiotics are the mainstay of therapy for RS, with tetracycline being the drug of choice. It is relatively low in toxicity, acts at an intracellular level, and is effective against spore formation under anaerobic conditions.[11] The tetracycline dose is 500 mg four times daily for a period of 6 months or until nasal biopsies are negative for the organism. (This may take up to several years.) Tetracyclines are contraindicated in pregnant females and in children, because of their effect on fetal development and bone formation. Other antibiotics that can be used include streptomycin sulfate, rifampin, sulfonamides, clofazimine, and second- and third-generation cephalosporins. Orally administered fluoroquinolones also appear to have excellent activity against gram-negative bacteria and low toxicity.[6] Early in our series, intravenous ampicillin appeared to have been an effective initial antibiotic, as determined by culture and sensitivity tests. Today the newer second- and third-generation cephalosporins would be a better choice of initial parenteral antibiotic.

Rhinoscleroma remains a difficult disease to treat because of the fact that the organism can remain dormant in an anaerobic spore form, only to be reactivated months to years later after the initial antibiotic treatment. In these patients, a decreased CD4/CD8 ratio has been observed, reflecting the inability of infected individuals to activate cells of the monocyte-macrophage system through cell-mediated immunity. This suggests that cell-mediated immunity may be defective in these patients.[12,13] This factor may be reflected as a poor host response to the bacterial invader, resulting in chronicity of the disease.[12] Serum immunoglobulin levels may mirror the body's response to the invading *K rhinoscleromatis* organism. It is currently believed that the humoral immunity remains intact and cellular immunity becomes impaired in patients with RS.[13] Patients in our study demonstrated increased IgA antibodies with nasal disease, progressing to increased IgG with LTS; 1 patient with LTS had a decreased CD4/CD8 ratio. That immunoglobulin levels normalized after successful treatment of these patients suggests a decrease in stimulation of their immune systems. These findings are not conclusive, however, as the numbers are small. Studies are currently under way to monitor the extent and reactivation of RS by using serum immunoglobulin levels.

In patients with acute airway obstruction, tracheostomy can be performed without any long-term sequelae. Most of the patients with LTS who developed respiratory symptoms had chronic stridor and mild dyspnea on exertion due to circumferential subglottic stenosis. In general, these symptoms do not improve significantly, despite long-term antibiotic therapy and treatment with steroids. Those patients who present with acute airway obstruction do so because of the edema superimposed on the underlying stenosis. In these patients, steroid therapy seems to be helpful, once a secure airway has been established through tracheostomy and antibiotic therapy has been instituted. Decannulation of these patients can be performed, provided the subglottic stenosis is not due to circumferential cicatricial scarring. In those patients, more extensive surgical therapy, such as tracheal resection and reanastomosis, may be warranted.[7,14] Dilation of the stenotic larynx has been described in the literature.[4,7] In our experience, dilation did not appear to affect the outcome. Laser therapy appeared to be effective only for isolated granulomatous lesions, and is of limited value in severe cicatricial stenosis.

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VOCAL FOLD SUBMUCOSAL INFUSION TECHNIQUE IN PHONOMICROSURGERY

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Phonomicrosurgery is optimized by maximally preserving the vocal fold's layered microstructure (laminae propriae). The technique of submucosal infusion of saline and epinephrine into the superficial lamina propria (SLP) was examined to delineate how, when, and why it was helpful toward this surgical goal. A retrospective review revealed that the submucosal infusion technique was used to enhance the surgery in 75 of 152 vocal fold procedures that were performed over the last 2 years. The vocal fold epithelium was noted to be adherent to the vocal ligament in 29 of the 75 cases: 19 from previous surgical scarring, 4 from cancer, 3 from sulcus vocalis, 2 from chronic hemorrhage, and 1 from radiotherapy. The submucosal infusion technique was most helpful when the vocal fold epithelium required resection and/or when extensive dissection in the SLP was necessary. The infusion enhanced the surgery by vasoconstriction of the microvasculature in the SLP, which improved visualization during cold-instrument tangential dissection. Improved visualization facilitated maximal preservation of the SLP, which is necessary for optimal pliability of the overlying epithelium. The infusion also improved the placement of incisions at the perimeter of benign, premalignant, and malignant lesions, and thereby helped preserve epithelium uninvolved by the disorder.

KEY WORDS — laryngoscopy, microlaryngoscopy, phonosurgery, vocal cord, vocal fold, voice.

INTRODUCTION

Phonomicrosurgery reflects the convergence of theories that guide endoscopic vocal fold surgery with theories that explain voice production.[1] The underlying premise of this surgical approach is that an optimal postoperative voice will be achieved if there is maximal preservation of the vocal fold's layered microstructure (laminae propriae and epithelium).[2,3] Toward this end, the concept of infusing saline and epinephrine into the superficial lamina propria (SLP) of the vocal fold was introduced in 1991.[4] Since that preliminary report, this technique has been used for a variety of vocal fold lesions. This investigation examined how, when, and why the infusion of saline and epinephrine into the SLP enhances phonomicrosurgical management of various vocal fold lesions.

MATERIALS AND METHODS

A retrospective review was performed on 152 phonomicrosurgical vocal fold procedures that were done during the past 2 years. Patients underwent a preoperative voice evaluation that included videostroboscopy, acoustic analysis, aerodynamic analysis, electroglottography, and subjective assessment.

The details of performing the suspension microlaryngoscopy have been described previously.[1,3,5] Submucosal infusion of the vocal fold was performed when it was judged to be an asset during dissection in the SLP and when it was felt that the lesion would not be obscured by the infusion-induced edema. If the submucosal infusion technique was selected, a specialized needle[4] was attached to a 3-mL Luer-Lok syringe that was filled with sterile saline and a concentration of 1/10,000 epinephrine. Typically, approximately 1 mL is infused; however, up to 3 mL has been placed during three infusions over 3 minutes with careful cardiac monitoring. The concentration of epinephrine was diluted to a concentration of 1/200,000 when the surgeon and anesthesiologist were concerned about hypertension and/or cardiac stability. The needle was carefully inserted into the SLP anterior to the vocal process on the superior surface of the fold. Care was taken to maintain the needle just under the translucent epithelium so as to minimize disturbance of the laminae propriae. The solution was infused until the musculomembranous vocal fold compartment was filled and saline began to back out of the puncture site. The saline distended the SLP and vibratory vocal fold epithelium and hydrodissected the mucosa (cover) from the underlying vocal ligament and muscle (body; Figs 1A,B, 2A,B, and 3A,B).

The majority of operations that were done with the submucosal infusion technique employed bimanual

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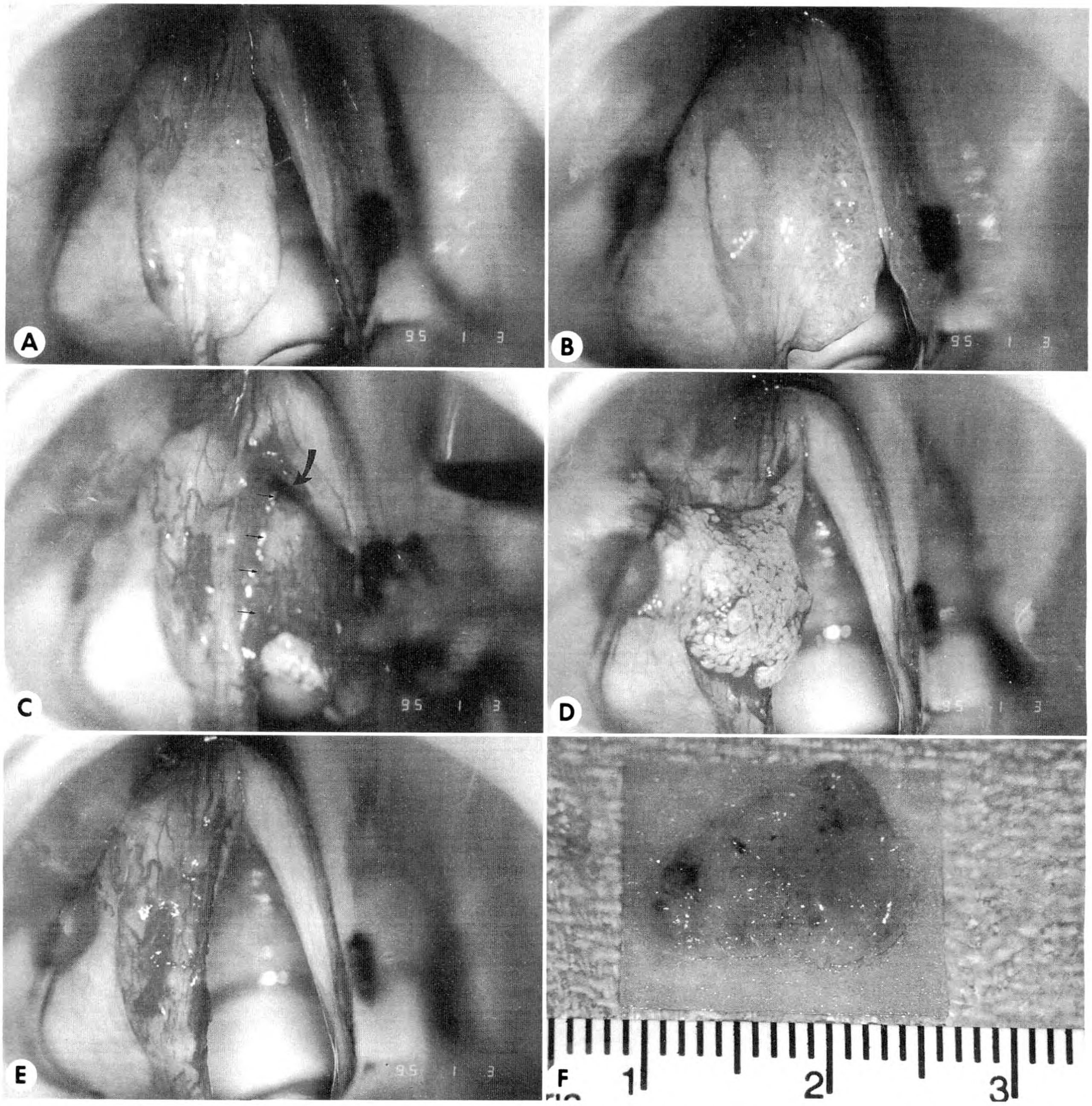

Fig 1. (Case 1) A) Extensive papillomatosis of left vocal fold. B) After submucosal infusion, microvasculature of superficial lamina propria (SLP) is vasoconstricted and there is improved exposure of ventricular-surface perimeter of lesion. C) Microflap containing lesion is being dissected. Left curved dissector (large arrow) adjacent to basement membrane of microflap is employed to sweep SLP (small arrows) back to patient. D) Microflap containing lesion is redraped to determine caudal extent of lesion for final excision. E) Lesion has been resected while maximally preserving normal SLP and epithelium; SLP and its microvasculature can be seen overlying white vocal ligament. F) Specimen has been placed on carrier for whole-mount section histopathologic analysis. (Continued on next page.)

cold-instrument dissection without the carbon dioxide laser.[6] Incisions in the epithelium and dissection in the laminae propriae were guided in such a way so as to minimally disturb normal tissue, especially on the medial vocalizing surface of the musculomembranous vocal fold. A wet cottonoid with 1/10,000 saline-epinephrine was placed gently over the fold as needed to aid in hemostasis and visualization. The details of the surgical resection of keratosis with atypia and cancer are described elsewhere.[1,3,7]

The cases that were selected for SLP infusion were stratified according to the underlying disorder: keratosis with atypia, cancer, hemorrhagic polyp, vocal nodule, cyst, papilloma, sulcus vocalis, granuloma, polypoid corditis (Reinke's edema), and anterior

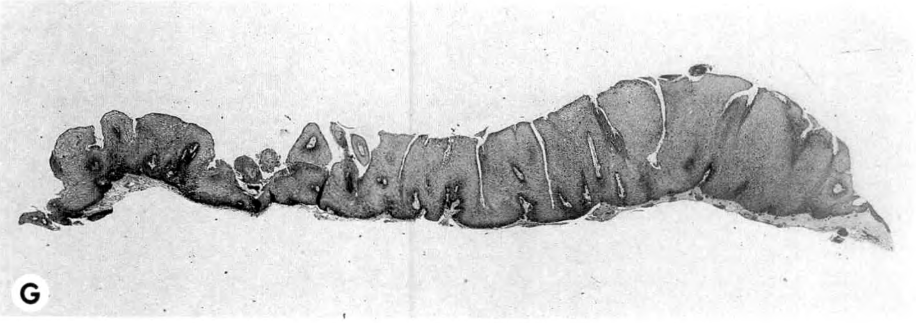

Fig 1 (continued). (Case 1) G) Histopathologic analysis (original ×14) of specimen that demonstrates that there is almost no SLP in specimen.

commissure web.

Postoperatively, patients were instructed to remain on absolute voice rest for 1 week if it was feasible, and subsequently, to practice vocal conservation for approximately 3 weeks. Those who demonstrated preoperatively either abusive vocal habits or generalized hyperfunction received vocal therapy postoperatively. Individuals who were suspected of gastroesophageal reflux were treated by means of diet and behavior modification, antacids, and medications; smokers were exhorted to discontinue smoking. Objective visual (videolaryngoscopy with stroboscopy), acoustic, and aerodynamic analyses were performed at least 6 weeks after surgery.

RESULTS

The distribution of vocal fold disorders for which 152 phonomicrosurgical procedures were performed is delineated in Table 1. Submucosal infusion of saline and epinephrine into the SLP of the vocal fold was done in 75 of the 152 procedures, and it facilitated the surgery in 73 of them. One small cyst and one small nodule became obscured by the submucosal infusion. The infusion technique was especially useful during the resection of an epithelial disorder that had relatively normal SLP underlying it (Table 1). This included cases of keratosis with atypia and respiratory papillomatosis (Fig 1), as well as some T1 carcinomas.

TABLE 1. DISTRIBUTION OF PROCEDURES

	With Submucosal Infusion	*Without Submucosal Infusion*
Keratosis with atypia	31	0
Cancer	8	0
Hemorrhagic polyp	10	18
Nodule	4	10
Cyst	4	8
Papilloma	15	0
Sulcus vocalis	3	0
Granuloma	0	4
Polypoid corditis (Reinke's edema)	0	34
Web	0	3
Total	75	77

The submucosal infusion helped identify which vocal fold disorders demonstrated an abnormal SLP and adherence of the basement membrane to the vocal ligament (medial and deep laminae propriae). Adherence of the epithelium of the musculomembranous vocal fold to the underlying ligament and muscle reflected a variety of pathologic processes (Table 2). Most commonly, the epithelial adherence was the result of scarring that was induced by previous microsurgery. This was noted in 5 of 8 cases of keratosis with atypia, 2 of 6 cancer cases, and 12 of 12 papilloma cases. The submucosal infusion helped to define and preserve any residual normal SLP. In the other 3 cases of keratosis with atypia and epithelial adherence, radiation fibrosis had replaced the SLP in 1 and chronic vocal hemorrhage had induced fibrosis in the other 2. The SLP was replaced by invasive carcinoma in 6 of the 8 cancer cases. Of those 6 cases, 2 were associated with previous microsurgery and 4 demonstrated direct invasion. Adherence of the base of the sulcus vocalis to the vocal ligament is a reflection of the natural history of that process.[8]

Results from comparisons of preoperative versus postoperative objective assessments of vocal function will be presented in future reports when there are sufficient data to allow valid stratification according to both the type of disorder and the size of the lesion.

DISCUSSION

The submucosal infusion technique described above arose from previous anatomic experiments that were performed in the 19th and mid-20th centuries. In the 1890s, Hajek[9] and Reinke[10] were concerned about mechanisms of laryngeal airway obstruction secondary to infectious-membranous aerodigestive tract disease. They performed laryngeal infusion experiments to simulate lethal obstructive processes that they were encountering clinically. As a result of these experiments, they began defining the connective tissue compartments of the larynx. The submucosal compartment of the musculomembranous vocal fold still bears Reinke's name. Later, Pressman

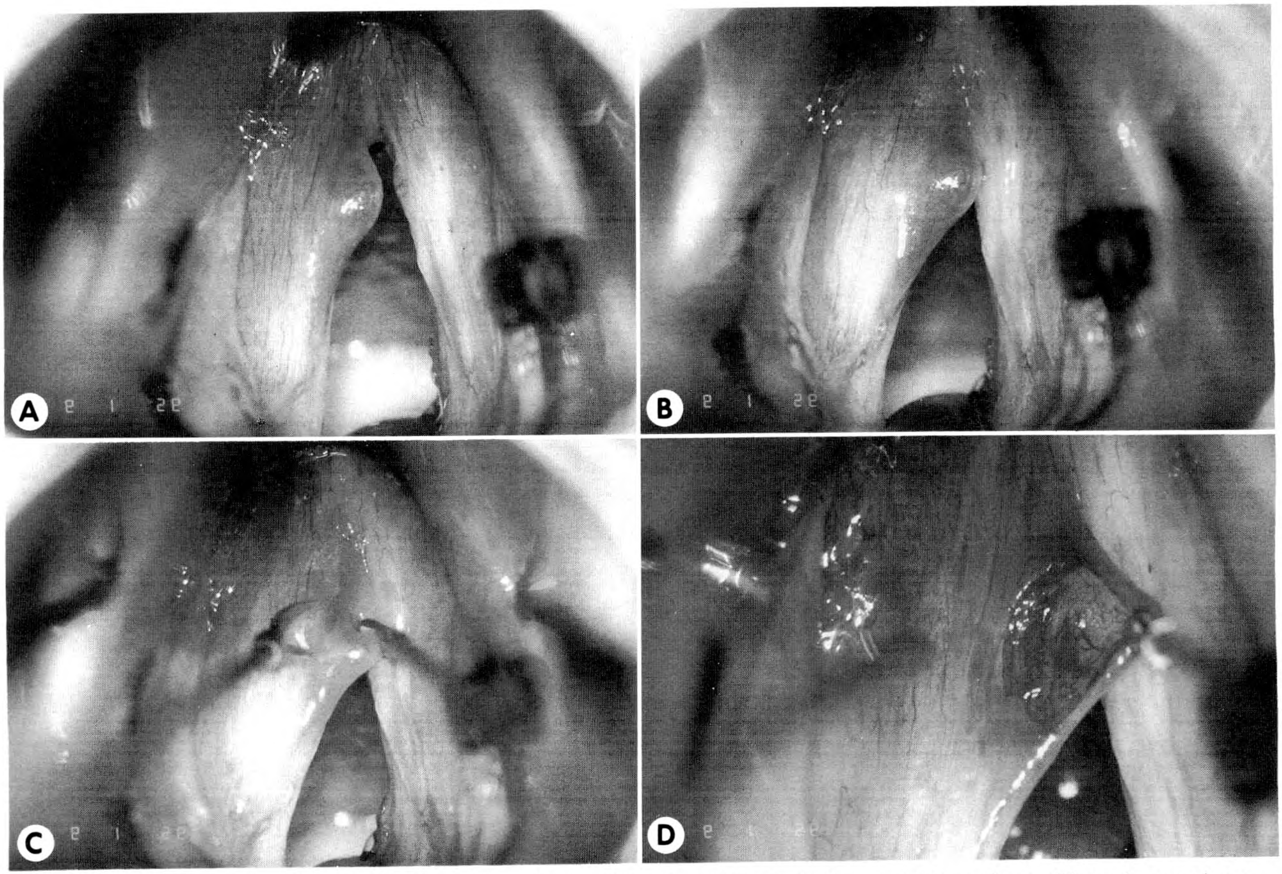

Fig 2. (Case 2) A) Small hemorrhagic polyp and contralateral nodule in rhythm and blues singer. There is prominent microvasculature in SLP. B) After infusion, microvasculature is vasoconstricted and depth of SLP has been increased. C) Incision is made on superior surface of vocal fold to remove lesion while preserving normal epithelium and SLP. D) Submucosal resection of lesion has been performed that maximally preserved vocal fold cover.

et al[11,12] and Welsh et al[13] repeated the investigations in a similar fashion. Their purpose, however, was to understand mechanisms of cervical lymphatic metastasis from the glottis.

The application of these experimental techniques for use in a surgical procedure was developed in the late 1980s. It evolved from two key observations: 1) that it was easier to resect atypia and early carcinomas that occurred along with polypoid corditis and 2) that the resulting voice was better than expected. Submucosal infusion[4] into the SLP[2] utilized prior experimental procedures to create a surgical environment similar to that of Reinke's edema. More recent experiments helped to establish the fact that the pliable vocalizing epithelium is typically hydrodissected by the submucosal infusion.[1]

It has been shown that the submucosal infusion technique facilitated maximal preservation of the three-dimensional microstructure of the vocal fold during extensive phonomicrosurgical resection of neoplastic epithelium and thereby resulted in a normal conversational-level voice.[1] This investigation applied the surgical concept of submucosal infusion to help establish appropriate indications for use of the technique for benign lesions.

The use of submucosal infusion of saline and epinephrine into the musculomembranous vocal fold enhanced the phonosurgical treatment of a variety of vocal fold disorders in a number of ways. Incisions into the vocal fold epithelium were facilitated because 1) the pliable epithelium was placed under greater tension, 2) the exposure for perimeter incisions around papilloma (Fig 1A,B), as well as neoplastic epithelium, was improved, and 3) the epinephrine solution caused vasoconstriction of the microvasculature of the SLP, which improved hemostasis and visualization.

Tangential dissection of both epithelial lesions (Fig 1C) and lesions that arose within the SLP (Figs 2 and 3) was enhanced by the epinephrine that was placed in Reinke's space. The submucosal infusion also increased the depth of the SLP, allowing for less instrumental trauma of the delicate elastic tissue of the SLP and thereby facilitating maximal preservation of the laminae propriae. Additionally, if the carbon dioxide laser was used, the infusion enhanced the dissection by acting as a heat sink, and helping prevent thermal trauma of the delicate vocal fold

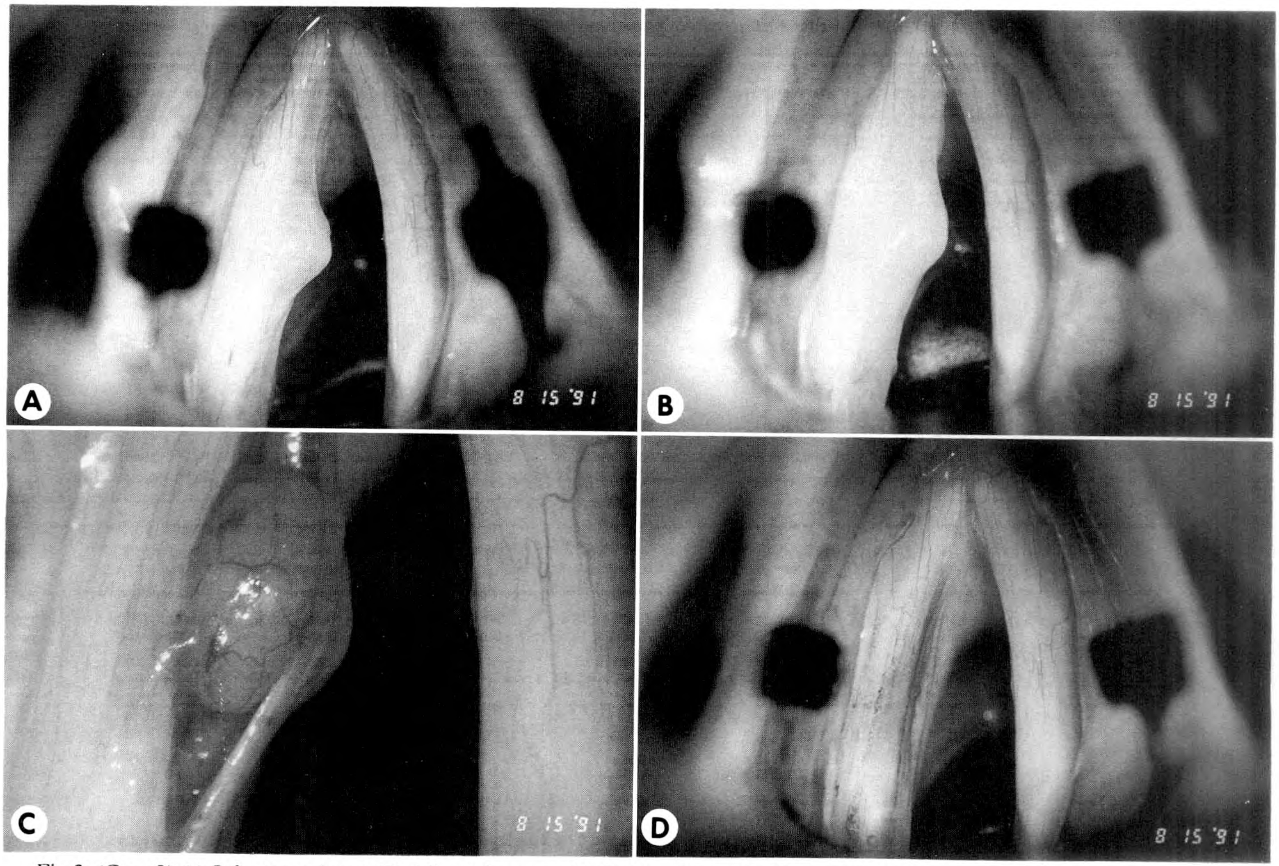

Fig 3. (Case 3) A) Submucosal cyst. B) After submucosal infusion, microvasculature of SLP is vasoconstricted. C) Microflap is performed to resect cyst. Improved hemostasis and visualization allowed for precise microflap dissection and avoidance of microvasculature of cyst wall. D) After excision of cyst, microflap redrapes naturally and it is difficult to see incision.

tissues.

The observations noted above explain how submucosal infusion of saline and epinephrine into the SLP enhanced precision during phonomicrosurgery. This precision allowed for maximal preservation of both normal SLP and epithelium. The most critical goal in performing phonomicrosurgery is to preserve normal SLP, because the loose elastic tissue does not regenerate after it is removed. Regeneration of normal epithelium has not been a problem in the majority of patients. Ultimately, the flexible oscillation of the regenerated epithelium is based on preservation of the underlying normal SLP.[1,8,14]

The flexibility of the vocal fold cover (epithelium and SLP) is critical for normal voice production.[15] As increasing stiffness occurs from loss of the elastic SLP, higher subglottal driving pressures are necessary to oscillate the glottal valve. Accordingly, stiffness of the vocal fold cover leads to impaired acoustic capabilities, as measured by maximal range tasks for intensity (loudness) and frequency (pitch), by frequency stability (jitter), and by loudness stability (shimmer).[1] The stiffness can be observed visually during stroboscopy as impaired mucosal wave propagation.

An optimal vocal result is achieved when the vocal folds' layered microstructure (Figs 1E, 2D, and 3C) is maximally preserved. This type of phonomicrosurgical precision is enhanced by vocal fold infusion of saline and epinephrine into the SLP. The validity of these concepts has already been demonstrated by means of objective vocal outcome data in one of the most difficult patient populations: those with premalignant epithelium and microinvasive cancer of the vocal fold.[1] The goal of this work was not to substantiate these concepts, but rather, to develop appropriate broader applications for using the submucosal infusion method. There are many lesions that can be managed equally well with and without the infusion, and success is related primarily to the individual surgeon's technique. The vocal outcome results from the preoperative and postoperative analyses are currently being accrued so that we can report meaningful information in the future that is based on larger cohorts that are stratified by both lesion size and specific disorder.

Application of Submucosal Infusion Technique. Lesions that were confined to the vocal fold epithelium (papilloma, neoplastic mucosa) were ideally suited for the SLP infusion technique (Table 1).

TABLE 2. EPITHELIAL ADHERENCE TO VOCAL FOLD BODY

	No. of Cases	*No. With Adherence*	*Cause of Adherence* *Surgical Scarring*	*Radiotherapy*	*Natural History*	*Chronic Hemorrhage*
Keratosis with atypia	31	8	5	1		2
Cancer	8	6	2		4	
Sulcus vocalis	3	3			3	
Papilloma	15	12	12			
Total		29	19	1	7	2

Frequently, the infusion could be placed between the epithelial basement membrane and the SLP, to allow for an almost bloodless and precise dissection that maximally preserved the laminae propriae. Bubbles from the turbulent infusion could often be seen under the epithelium (Figs 1B and 2B). Despite extensive resection of the vocalizing epithelium, postoperatively, the patient would typically have a normal conversational-level voice, measured both objectively and subjectively.[1]

Submucosal infusion of the SLP facilitated excision of some cysts (3 of 8; Fig 3) and nodules (3 of 10; Table 1). Typically, excision of larger lesions was enhanced, while visualization of smaller lesions was obscured. Small (< 3 mm) hemorrhagic polyps could be managed equally well with or without the infusion (Fig 2). Excision of medium-sized polyps (3 to 8 mm) was usually enhanced by the infusion because of vasoconstriction of the microvasculature feeding the polyp. The infusion was not used in large hemorrhagic polyps, because the exposure for placing the infusion was problematic and because hemostasis was obtained with the use of a microspot carbon dioxide laser. With sulcus vocalis, the submucosal infusion helped both to define the exact limits of the lesion and to allow for ease in hemostatic cold-instrument dissection in the SLP. The infusion technique was not used during the excision of webs and granulomas, as there was usually no need to preserve laminae propriae. As expected, SLP infusion was not employed during the surgical management of polypoid corditis, because there already was extensive swelling in Reinke's space.

Epithelial Adherence to Vocal Fold Body. Submucosal infusion into the musculomembranous vocal fold helped identify when and where the SLP was scarred and/or absent. In the presence of a normal SLP, the infusion hydrodissected the epithelial basement membrane away from the vocal ligament and increased the depth of the SLP. Abnormal scarring and stiffness of the SLP was demonstrated by adherence of the vocal fold epithelium to the underlying microstructure. The geographic localization of the scarred SLP could then be mapped. This three-dimensional assessment of the vocal fold microstructure has previously helped explain and predict the vocal outcome after phonomicrosurgery.[1]

There were a variety of clinical settings in which there was a loss of normal SLP. This occurred when the infusion failed to hydrodissect the vocal fold epithelium from the medial lamina propria, resulting in abnormal adherence of the epithelium to the underlying vocal ligament (Table 2). This finding was noted in 29 of the 75 cases in which the submucosal infusion technique was used. Abnormal adherence of the epithelial cover to the underlying body of the vocal fold was most likely due to surgical scarring; however, fibrosis from radiotherapy and chronic vocal hemorrhage was also noted. Loss of the SLP was to be expected as part of the natural history of invasive vocal fold cancer and sulcus vocalis.

CONCLUSIONS

Phonomicrosurgical management of the musculomembranous vocal fold is optimized by maximally preserving the vocal folds' layered microstructure, which is necessary for optimal pliability of the epithelium. Submucosal vocal fold infusion of saline and epinephrine helped achieve this goal for a variety of benign and malignant disorders in a number of ways. It did so by vasoconstricting the microvasculature in the SLP, allowing for improved visualization during cold-instrument tangential dissection. The infusion also improved the placement of incisions at the perimeter of benign, premalignant, and malignant lesions, and thereby helped preserve epithelium uninvolved by the disorder. The submucosal infusion technique was most helpful when the vocal fold epithelium required resection and/or when extensive dissection in the SLP was necessary.

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FRAGMENTED, DISTORTED CRICOID CARTILAGE: AN ACQUIRED ABNORMALITY

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This paper reports the identification of the fragmented, distorted cricoid cartilage. The laryngeal findings in four patients with this acquired abnormality are presented. The postmortem whole organ serial section of their larynges is described and illustrated with horizontal sections from the Laryngeal Development Laboratory in Chicago. The histopathologic sequence, pathogenesis, and clinical relevance are elucidated.

KEY WORDS — acquired subglottic stenosis, cricoid cartilage, laryngotracheal stenosis.

INTRODUCTION

Congenital subglottic stenosis has long been recognized as a potential cause of airway obstruction in neonates and infants.[1] In the past 25 years, acquired subglottic stenosis secondary to long-term intubation has proved even more challenging. Acquired laryngeal stenosis differs from congenital stenosis in that it is a complication of medical treatment, and it is generally more severe, requiring more creative and invasive intervention.

Subglottic stenosis may be classified in three ways: 1) etiologic (congenital or acquired), 2) clinical or anatomic (hard or soft), and 3) histopathologic.[2] The histopathologic classification of subglottic stenosis is presented in Table 1.[2] Abnormalities of the cricoid cartilage form the major subgroup of congenital subglottic stenosis. While acquired subglottic stenosis is readily diagnosed by most otolaryngologists, it is the scarring of fibrous, cicatricial stenosis, ie, the soft tissue acquired stenosis (submucosal fibrosis and glandular hyperplasia), that is most commonly understood. The histopathology of acquired cartilaginous subglottic stenosis with distortion and fragmentation of the cricoid cartilage has been recently described.[2]

MATERIAL AND METHODS

Four postmortem larynges with fragmented, distorted cricoid cartilages have been identified in the collection of the Laryngeal Development Laboratory at The Children's Memorial Hospital, Chicago, Illinois. The specimens were preserved and processed according to the protocol developed by Tucker et al.[3] They were embedded in pyroxylin (Parlodion) and sectioned at 28 μm in the horizontal plane from top to bottom, with every 20th section mounted as part of a tracer series. Data were sought regarding the patients' age, sex, clinical history, timing and size of endotracheal intubation, tracheostomy, and findings and

TABLE 1. PATHOLOGIC CLASSIFICATION OF SUBGLOTTIC STENOSIS

- Cartilaginous stenosis (usually congenital)
  - Cricoid cartilage deformity (stenosis)
    - Normal shape, small size
    - Abnormal shape
      - Elliptical shape
      - Cleft: partial, occult (submucosal), complete
      - Flattened shape
      - Other, including acquired lesions
        - Fragmented, distorted cricoid
        - Cricoid ossification
        - Thickened cricoid
  - Trapped first tracheal arch
- Soft tissue stenosis (usually acquired)
  - Submucosal mucous gland hyperplasia
  - Ductal cysts
  - Submucosal fibrosis (fibrous connective tissue)
  - Granulation tissue

Information from Chen and Holinger.[2]

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TABLE 2. CLINICAL DATA SUMMARY

Case No.	*Age*	*Sex*	*Duration of Intubation (d)*	*Multiple Intubations*	*Size of Endotracheal Tube*	*No. of Endoscopic Dilations*	*Duration of Tracheostomy*	*Gestation*	*Gastroesophageal Reflux*
1	10.5 mo	M	60	Yes	3.5	5	9 mo	32 wk	No
2	2.5 mo	F	55	Yes	4.0, 3.5, 3.0	2	22 d	34 wk	Yes
3	19 mo	M	8	Yes	3.0	13	11 mo	Term	No
4	9 y	F	14	Yes	6.5	None	30 d	Term	No

frequency of endoscopic examinations and other procedures. The following case report is representative of the usual clinical course. Individual details are reported in Results and Table 2.

CASE REPORT

In case 1, a 10½-month-old, premature (32-week gestation, birth weight 1,720 g) male infant suffered severe asphyxia neonatorum (Apgar scores were 1 and 2 at 1 and 5 minutes), necessitating intubation since birth. He had a history of recurrent seizures and apnea probably due to anoxic brain insult. Because he failed extubation attempts, the infant was transferred to Children's Memorial Hospital in Chicago at age 2 months. The operative report of the laryngoscopy

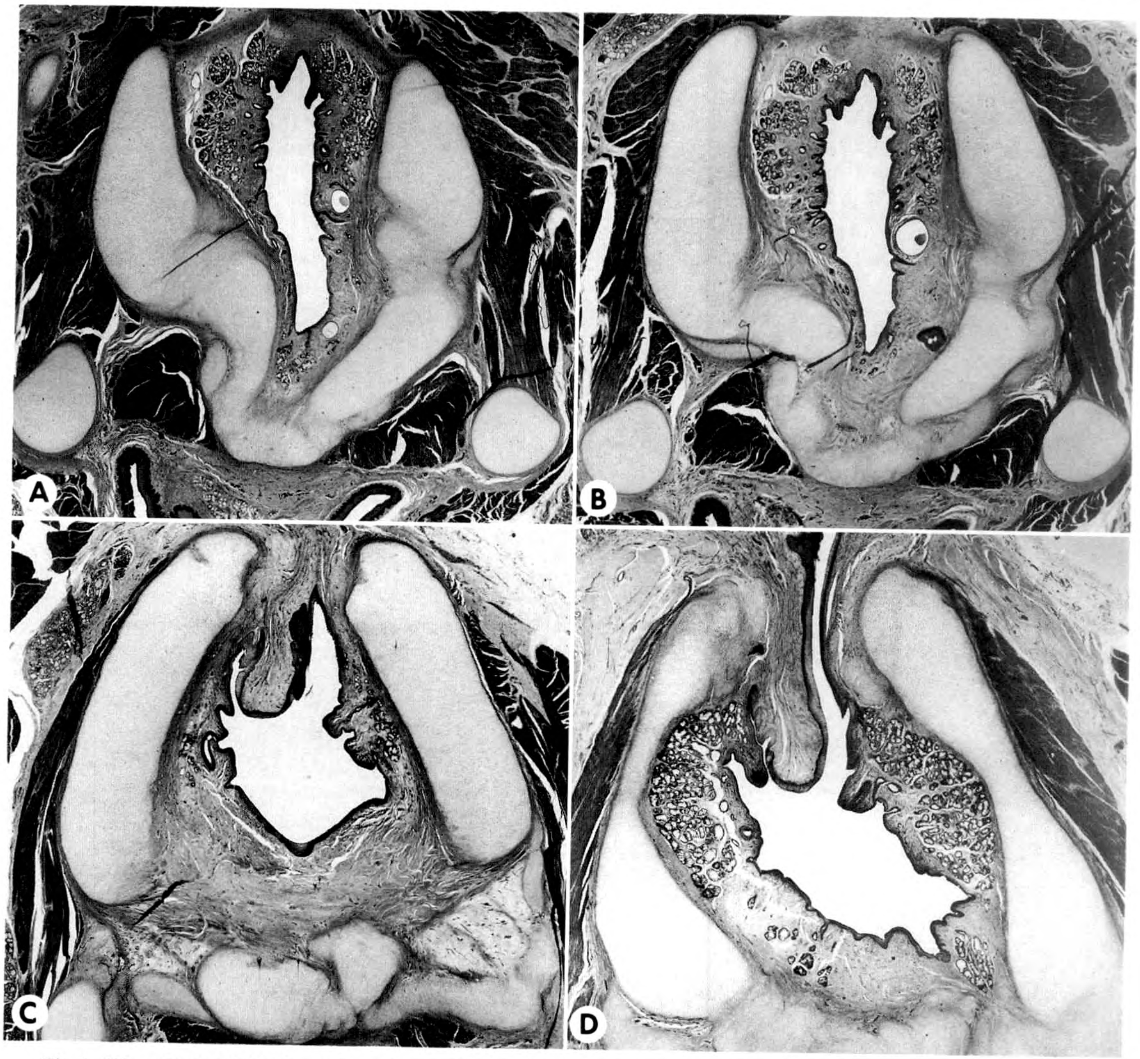
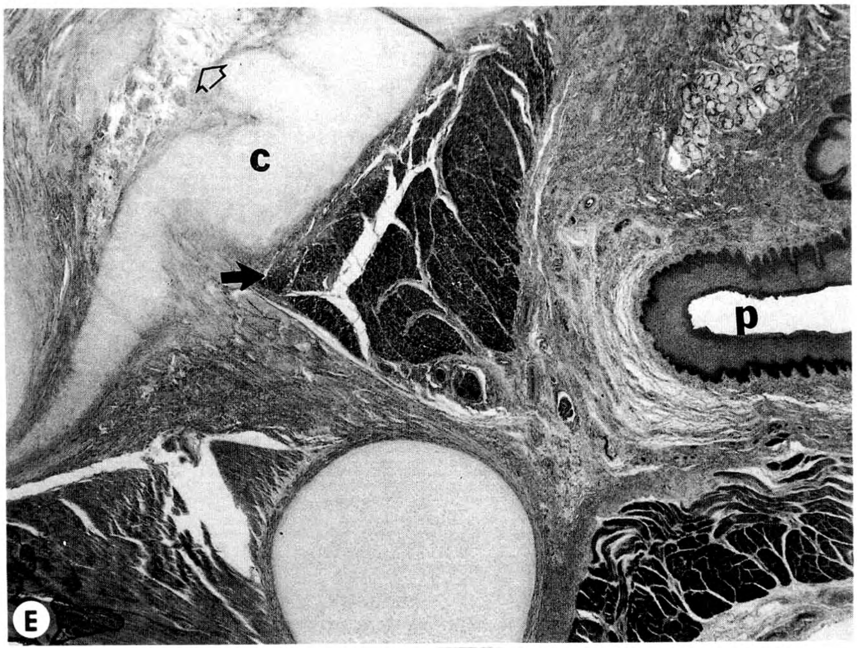


Fig 1. (Case 1) A-D) Horizontal sections of larynx from most superior section (midcricoid, A) to most inferior (lower cricoid, D; H & E). Shows distortion of cricoid lamina posteriorly (A-D) with elliptical shape (A,B). Anterior changes in C and D represent injury to anterior cricoid lamina that may have occurred during tracheostomy. Laryngeal lumen is stenotic. Submucosal fibrosis and glandular hyperplasia are also apparent. (Continued on next page.)



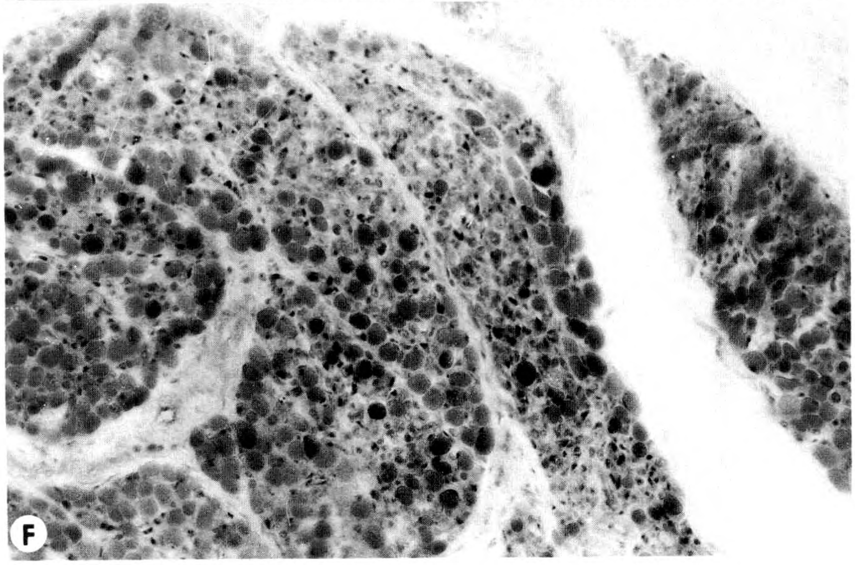


Fig 1, continued. E) High-power view showing irregularly shaped cricoid cartilage (c; H & E, original ×25). Surrounding structures show evidence of tissue regeneration after presumably posttraumatic injury, namely, loosely textured, early granulation tissue encroaching on perichondrium (open arrow), and rarefied muscle bundles (solid arrow) in contact with deformed cartilage. p — lumen of pharynx. F) Higher magnification of muscle bundles from area marked by solid arrow in E (H & E, original ×100). Muscle fibers appear separated from each other by abundant nuclei of endomysial cells, indicative of regeneration.

following admission documents severe subglottic stenosis and an appearance suggestive of a laryngeal cleft. Tracheostomy was accomplished and he was maintained on a ventilator. Laryngoscopy and laryngeal dilation of the subglottic area was carried out on four occasions. The child died suddenly of recurrent seizures 3 months after his last endoscopic procedure.

Laryngeal sections show distortion of the cricoid lamina posteriorly with an elliptically shaped cricoid (Fig 1A-D). Changes to the anterior cricoid lamina probably represent injury from retraction that occurred during tracheostomy. The laryngeal lumen is stenotic. Submucosal fibrosis and glandular hyperplasia are apparent. Tracheal sections show diffuse squamous metaplasia, as is characteristic with tracheostomy.

RESULTS

All four cases of fragmented, distorted cricoid were identified on postmortem horizontal laryngeal sections, one of which also had an elliptical cricoid. There were two boys and two girls. The age at time of death ranged from 2.5 months to 9 years. All had been intubated during life. Two were born premature. Three had required intubation immediately postpartum. The duration of intubation ranged from 8 days to 2 months. The sizes of endotracheal tubes used were appropriate for their age during life, except in case 2, in which size 4.0 may have been marginally large.[4] Most had trauma from repeated intubations. Clinically, subglottic stenosis was suspected because of extubation failure.

The diagnosis was confirmed during endoscopy.

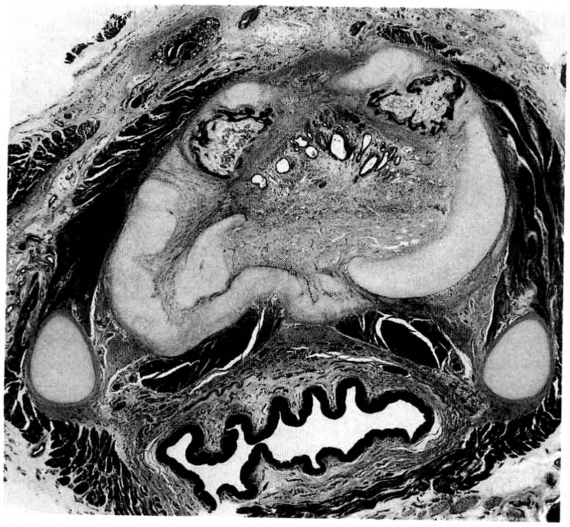


Fig 2. (Case 2) Distortion and fragmentation of cricoid cartilage (H & E). Ossification of cricoid cartilage is evident. Laryngeal lumen is completely stenosed, with extensive submucosal fibrosis.

Three of the four patients had multiple laryngoscopies and dilations. All had undergone tracheostomy. The duration of tracheostomy ranged from 22 days to 11 months. Only one patient had documented associated gastroesophageal reflux.

Laryngeal sections of the patient in case 2, an 11-week-old premature infant, show extensive submucosal fibrosis (Fig 2). There is distortion and fragmentation of the cricoid cartilage. Ossification of the cricoid cartilage is evident. The laryngeal lumen is completely stenosed. Tracheal sections show squamous metaplasia.

Laryngeal sections of case 3 show the posterior cricoid lamina to be grossly distorted except in its upper portion (Fig 3). The rim of the cricoid is thick, and in the latter sections there is fragmentation and sequestration of the cartilage, especially in the right posterior quadrant. In the superior rim of the cricoid cartilage there is ossification anteriorly and posteriorly. Other abnormalities include marked stenosis of the laryngeal lumen, dense submucosal fibrosis, and glandular hyperplasia.

Laryngeal sections of case 4 show a flattened cricoid (Fig 4). There is distortion of the posterior upper cricoid lamina, a trapped first tracheal arch, and an isolated island of cartilage. There was also submucosal fibrosis and glandular hyperplasia.

DISCUSSION

Congenital Cricoid Abnormalities. A brief review of congenital cricoid abnormalities brings into perspective the fragmented, distorted cricoid (Table 1). Congenital anomalies include the small cricoid,[5] elliptical cricoid,[6] flattened cricoid, thickened cri-

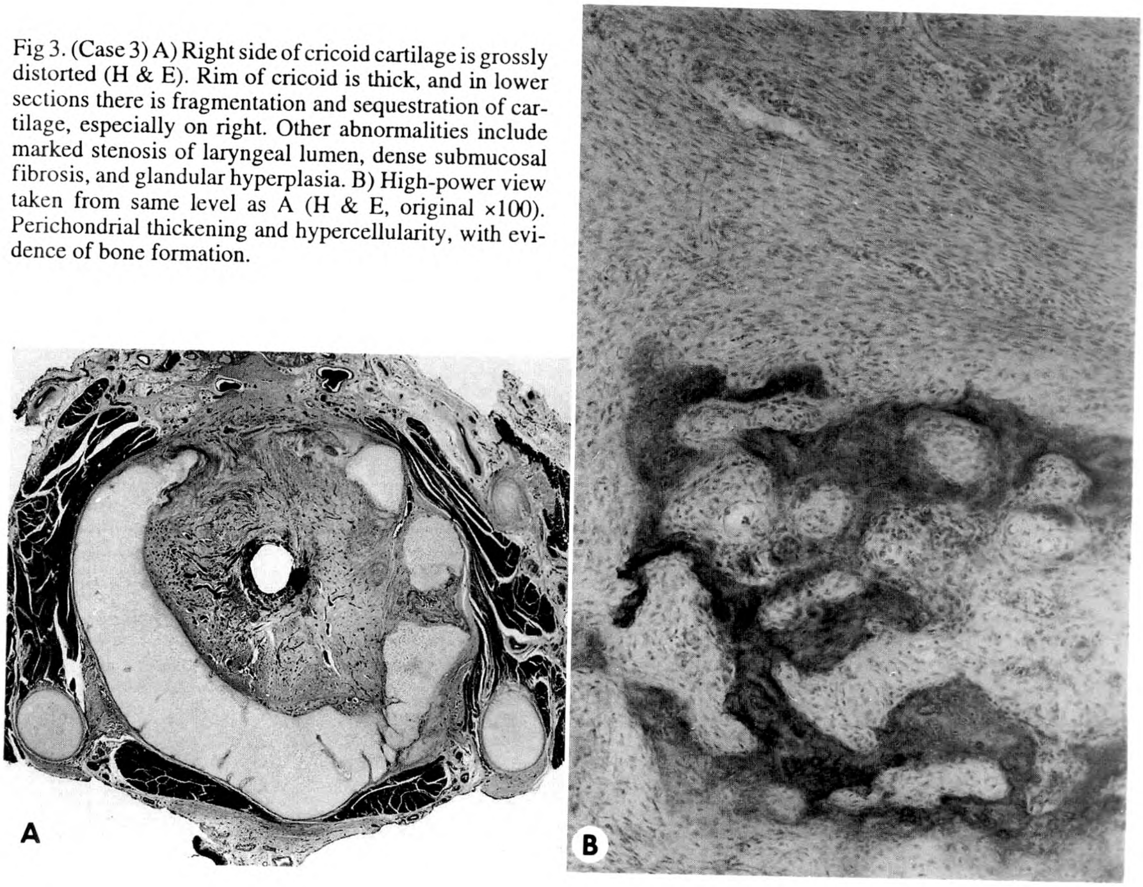


Fig 3. (Case 3) A) Right side of cricoid cartilage is grossly distorted (H & E). Rim of cricoid is thick, and in lower sections there is fragmentation and sequestration of cartilage, especially on right. Other abnormalities include marked stenosis of laryngeal lumen, dense submucosal fibrosis, and glandular hyperplasia. B) High-power view taken from same level as A (H & E, original ×100). Perichondrial thickening and hypercellularity, with evidence of bone formation.

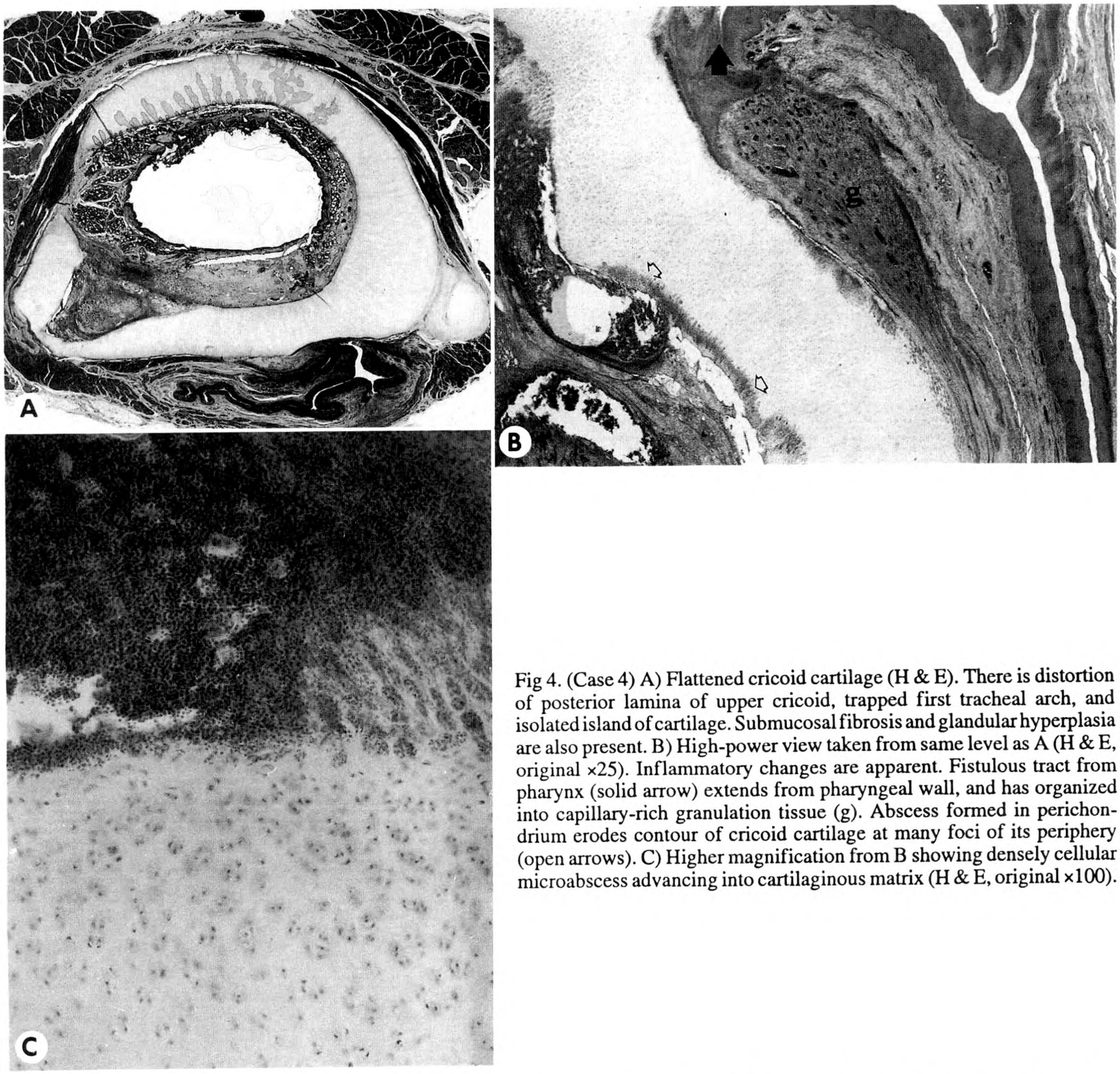


Fig 4. (Case 4) A) Flattened cricoid cartilage (H & E). There is distortion of posterior lamina of upper cricoid, trapped first tracheal arch, and isolated island of cartilage. Submucosal fibrosis and glandular hyperplasia are also present. B) High-power view taken from same level as A (H & E, original ×25). Inflammatory changes are apparent. Fistulous tract from pharynx (solid arrow) extends from pharyngeal wall, and has organized into capillary-rich granulation tissue (g). Abscess formed in perichondrium erodes contour of cricoid cartilage at many foci of its periphery (open arrows). C) Higher magnification from B showing densely cellular microabscess advancing into cartilaginous matrix (H & E, original ×100).

coid,[7] and abnormally shaped cricoid associated with a laryngeal cleft.[8,9] The most severe congenital cricoid cartilage abnormalities are usually associated with cleft larynx. The cricoid cartilage of the cleft larynx is typically C-shaped, open in the midline posteriorly.[8] The cricoid cartilage of the partial cleft larynx is intact inferiorly. The interarytenoid muscle is interrupted, and there is continuity of respiratory and hypopharyngeal mucosa. The occult posterior laryngeal cleft, first described by Tucker and Maddalozzo,[9] consists of an incomplete submucous cleft of the cricoid cartilage with intact soft tissue including the interarytenoid muscle. Congenital distortions of the cricoid are less severe than the acquired distortions and fragmentation reported herein.

Acquired Cricoid Abnormalities. The fragmented, distorted cricoid cartilage occurs with the most severe acquired laryngeal stenosis. The sequence of histopathologic events leading to this stenosis involves the following steps[10]: 1) ulceration, 2) healing of ulcers, 3) fibrous tissue formation, and 4) cartilage injury and healing.

The earliest laryngeal injury produced by an endotracheal tube is ulceration, which may take the form of abrasion and superficial ulceration or pressure necrosis and full-thickness ulceration. Abrasion and superficial ulceration may leave the basement membrane of the epithelium intact, or may be deeper, with some degree of destruction of underlying connective tissue. This superficial ulceration is not obvious macroscopically. Endoscopically, it may appear as a topical color change of the mucous membrane.[11] Pressure necrosis may lead to a slow dissolution of compressed tissue[12] by direct pressure or through the mechanism of ischemia. Ischemia occurs when pressure exerted by the endotracheal tube exceeds mucosal capillary pressure. The compressed ischemic mucous membrane necroses, then exfoliates. The direct compression–induced necrosis and ischemia-induced necrosis usually act together to cause deep ulceration of the laryngeal mucous membrane. With time, infection, or both,[13,14] the ulceration becomes more extensive, penetrating the perichondrium and cartilage, causing perichondritis and frank chondritis (Fig 4B,C). Clinically, full-thickness ulceration to the cartilage is common.[15] Endoscopic examination reveals exposed white, shining cartilage in "ulcerated troughs," discussed by Benjamin.[16] These troughs occur in two locations: 1) in the subglottic larynx, as craniocaudal lines on the upper posterior lamina of the cricoid, and 2) on the medial surface of the vocal process of the arytenoid cartilages. In extreme cases, ulceration may occur in the posterior glottis and interarytenoid region,[17] even as annular ulcerations, rarely involving the entire circumference of the cricoid ring.

The ulcer undergoes an inflammatory process resulting in either primary or secondary healing. Primary healing with squamous metaplasia or hyperplasia occurs with regeneration of epithelium proceeding from the basement membrane. Little collagen deposition and scarring takes place.[12] The lost epithelium heals normally. This superficial ulceration is relatively unimportant clinically.

When the ulceration of the mucous membrane involves underlying connective tissue as well as epithelium, secondary healing takes place. This involves granulation tissue and subsequent fibrous tissue formation. Contraction of collagen in this fibrous scar results in "healed furrows."[16] Exposed cartilage acts as a foreign body, causing excessive granulation tissue and collagen deposition.[18] Most exuberant granulation tissue resolves without sequelae.[17] Certain injuries produce considerable fibrous scar tissue, which leads to the complications of laryngeal stenosis; host-specific responses contribute to various degrees in individual patients as detailed below.

As time passes, inflammatory cells gradually subside. Collagen fibers gain strength and replace granulation tissue. Healed fibrous nodules[16] may form at the vocal process of the arytenoids. Accumulation of submucosal fibrous tissue results in airway obstruction in glottic and subglottic airways. Contraction of scar tissue also causes distortion of the glottis and the cricoid cartilage.

Cricoid cartilage necrosis with collapse of the cartilage framework of the larynx may be an essential component in the development of subglottic stenosis.[19-21] This concept has received support from animal studies.[22,23] Perichondritis occurs on the arytenoid and cricoid cartilages from the third day of intubation. Perichondritis of the arytenoids, as well as ulceration of the arytenoids and cricoid cartilage, almost invariably occurred by 96 hours of intubation.[11,24] The presence of acute full-thickness cricoid necrosis in an infant intubated for 5 days demonstrates the rapidity with which severe injury can occur.[15] Severe injury to the laryngeal cartilages is an early complication; prolonged intubation, on its own, is unlikely to produce subglottic stenosis.[15]

When inflammation involves the cartilage, the severity of this inflammation may be enough to cause dissolution of chondroid matrix, with subsequent distortion and fragmentation. Dilation and other factors may also play a role. The cricoid cartilage undergoes progressive necrosis, extending from the inner cartilaginous surface to the outer.[22] Following intubation injury to the laryngeal cartilages, healing usually occurs during the second and third weeks of intubation, even in the continued presence of the endotracheal tube.[15] By 2 weeks after experimental injury in dogs, the perichondrium appears disrupted and the necrotic cartilage is actively replaced by new cartilage formation.[13] Fibrous tissue may fill the gaps left by the necrotic cartilage and proliferate in the direction of the tracheal lumen.[22] If healing is interfered with, as by persistent inflammation, the result may be a grossly misshapen cartilage. Ossification of the cricoid cartilage likewise seems to be a feature indicative of severe cartilage injury (Fig 2).

During the last two decades, considerable importance has been attributed to the "myofibroblast," a cell that combines the features of the fibroblast and smooth muscle cell, and which was first identified in contractile granulation tissue.[25,26] The contractile properties of these cells may contribute to the shrinking of scars. It is likely that distortion of the cricoid is at least partly the result of healing and fibrosis.[13]

The proliferative phase of repair may result in soft stenosis without cartilaginous involvement and a compromised airway. The reparative process occasionally leads to resolution of the stenosis following the establishment of an adequate upper airway by tracheostomy. Alternatively, it may progress to form a hard stenosis of mature fibrous tissue.

Etiology of Acquired Laryngeal Stenosis. There is no clear evidence of a single principal cause of laryngeal stenosis. Several factors are probably responsible, and their effects are probably synergistic. The primary site of most damage is within the cricoid ring, the narrowest part of the upper airway in the neonate and child, and the only point at which the airway is surrounded completely by cartilage. Many factors contribute to intubation injury. In any individual patient one or more may play a role. The relative significance of each is difficult to determine.

Endotracheal tube factors include 1) tube size, shape, composition, and texture, 2) duration of intubation, 3) traumatic or repeated intubation, and 4) movement of the endotracheal tube. Trauma to the mucosa and cartilage from continuous pressure of a relatively large tube, as described above, causes ischemic necrosis of the mucous membrane and cartilage. This process is presumably worse, the tighter the fit. Silicone rubber and polyvinyl chloride are considered the safest for long-term intubation. Tube size may be the most important factor in most patients.[27] The relative importance of duration of intubation is controversial and unresolved. In regard to traumatic or repeated intubation, each passage of the endotracheal tube increases the risk of mucosal injury.[28] The piston action of the respirator and the abrasive action of the tube against the mucosa during swallowing or in restless patients increases the likelihood of significant injury.

Patient factors include 1) the shape and size of the larynx, 2) subsequent tracheostomy, 3) infection and sepsis, 4) gastroesophageal reflux, 5) hypotensive episodes, which may predispose to ischemic necrosis, 6) wound healing and keloid formation, and 7) activity of the patient.

Congenitally small larynges are susceptible to injury by an endotracheal tube and are more likely to develop a secondary acquired stenosis.[29] Congenital subglottic stenosis may be associated with other congenital lesions and syndromes such as trisomy 21 (Down syndrome), which are known to have a high incidence of congenitally small larynx.[30] Three of the cases discussed herein were in premature infants who may have had a congenitally small larynx.

In subsequent tracheostomy, superimposed bacterial infection compounds the mechanical mucosal trauma by increasing the inflammatory response and scar tissue formation. The role of infection in the development of a stenosing lesion was investigated by Sasaki et al,[13] who concluded that tracheostomy-related infection of a mucosal injury of the subglottic lesion can progress to chondritis and subsequent stenosis. Strong and Passy[14] also reported that subglottic stenosis is twice as common in children when intubation is followed by tracheostomy. All four patients discussed had tracheostomy. One may have had direct surgical injury to the cricoid cartilage.

Gastroesophageal reflux may potentiate endotracheal trauma and complicate the healing process. Patients intubated in an intensive care unit setting have a high incidence of pharyngeal reflux.[31] Perfusion of the rabbit larynx with acid and pepsin produces severe inflammation.[32] Intermittent application of the gastric contents to the larynx in a dog model produces subglottic stenosis if a prior mucosal injury exists.[33] Intermittent reflux (three episodes per week) can result in severe laryngeal damage if there is prior mucosal injury.[31]

Diagnosis. Subglottic stenosis is a clinical endoscopic diagnosis that includes a variety of histopathologic conditions that produce narrowing of the subglottic airway.[6,34] It is important to define precisely the nature and extent in each individual to plan appropriate treatment. Radiologic studies are of little value in infants and children. The clinical diagnosis is made by direct laryngoscopy and palpation of the stenotic area to determine if it is hard or soft. A hard stenosis may be cartilaginous or a mature fibrous stenosis. A gentle attempt to pass a dilator through a hard stenosis helps to determine whether the lesion is a cartilaginous or a fibrous cicatricial stenosis.[35] Cartilaginous subglottic stenoses (either congenital or acquired) are not amenable to dilation.

Careful endoscopic evaluation provides important clues to the precise histopathology of laryngeal stenosis. However, the actual determination of the gross pathologic diagnosis cannot be made until the time of laryngotomy for reconstructive surgery. At postmortem examination the histopathologic changes themselves can finally be documented.

Treatment. Treatment of laryngeal stenosis requires identification and successful control of contributing factors such as gastroesophageal reflux. It also depends on the age of the patient and the type and location of stenosis. With time, the infant with congenital cartilaginous stenosis may eventually outgrow the problem. This is less likely to occur with acquired stenosis. The most severe stenoses, such as with a fragmented, distorted cricoid cartilage and 90% to 100% obstruction, will require surgical management such as laryngotracheal reconstruction with cartilage graft and stenting, or cricotracheal resection. Dilation is not effective. When the cricoid cartilage is severely distorted or fragmented, a cricotracheal resection or four-quadrant division of the cricoid will probably be required.[36]

CONCLUSION

The fragmented, distorted cricoid cartilage, a severe form of laryngeal stenosis, is described. The four cases described herein were acquired abnormalities, strongly suggesting that the fragmented, distorted cricoid cartilage is an acquired lesion.

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RECONSTRUCTION OF THE RABBIT TRACHEA WITH VASCULARIZED AURICULAR PERICHONDRIUM

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Success in laryngotracheal reconstruction has been limited, in part, by the lack of an ideal grafting material. Perichondrium is thin, pliable, and highly vascularized and has the ability to generate new cartilage providing rigid support. These qualities make vascularized perichondrium potentially the ideal grafting material for circumferential airway stenosis. A pedicled vascularized flap of auricular perichondrium was used in a rabbit model (n = 39) to reconstruct a near-circumferential tracheal defect without a tracheostomy. A stent was used to support the reconstructed airway for 6 weeks, after which time it was removed by direct laryngoscopy. Animals were observed for an additional 6 weeks prior to sacrifice. Qualitative and quantitative histologic analysis of neochondrogenesis is reported. Vascularized perichondrium and periosteum show promise as potential grafts for reconstruction of circumferential tracheal defects.

KEY WORDS — airway, chondrogenesis, perichondrium, reconstruction, stent, vascularization.

INTRODUCTION

The variety of grafts available for laryngotracheal reconstruction suggests that the ideal grafting technique has not yet been identified. Examples include hyoid bone, clavicle, rib, iliac crest, auricular cartilage, nasal septal cartilage, epiglottis, thyroid cartilage, and costal cartilage. While these grafts prove adequate for most repairs, they do not permit the extensive reconstructions needed in patients with long segments of cicatricial stenosis, complete airway obliteration, or loss of cartilaginous support. In addition, a variety of local and/or systemic conditions, such as diabetes, compromise the vascularity of the recipient bed, further limiting graft survival. Such cases of severe airway stenosis are the driving force behind the search for a highly reliable graft.

The ideal grafting material for the airway should be well vascularized, allowing it to become rapidly mucosalized and resistant of infection, resorption, and scarring once transferred to the contaminated airway environment. The graft should be rigid enough to support the airway, yet flexible enough to allow an airtight repair and conform to the airway defect. The repair should, ideally, be performed in a single stage with little or no need for intraluminal stenting. Finally, there should be an adequate supply of the grafting tissue such that its harvest confers minimal donor site morbidity.

Increasing expertise with microvascular tissue transfer has provided new potential sources of vascularized grafts for airway reconstruction. Vascularized perichondrium and periosteum are two tissues that possess many of the essential characteristics of the ideal graft. Both perichondrium and periosteum have a rich vascular supply and are available with minimal morbidity from multiple donor sites. Their pliability at the time of reconstruction allows for contouring and an airtight repair, yet they are ultimately capable of providing rigid support because of their intrinsic chondrogenic and osteogenic potential. Finally, both vascularized perichondrium and periosteum can be utilized with either a one-stage or two-stage approach to reconstruction.

Hartig et al[1] recently demonstrated that vascularized auricular perichondrium generates significantly more neocartilage than free auricular perichondrium when used to repair an anterior airway defect. Clevens et al,[2] using the same model, reported that the superior chondrogenic potential of vascularized perichondrium is not adversely influenced by the presence of an intraluminal stent or free mucosal graft. The purpose of our investigation was to test whether vascularized perichondrium can be used for reconstruction of larger segmental airway defects, and whether the

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From the Department of Otolaryngology–Head and Neck Surgery, University of Michigan, Ann Arbor, Michigan. Supported in part by a Research Training Grant in the Communicative Sciences from the National Institutes of Health (NIH #T32DC00024). This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Michigan and the Ann Arbor Veterans Administration Hospital.

Presented at the meeting of the American Laryngological Association, Palm Desert, California, April 29-30, 1995. Winner of the Resident Research Award.

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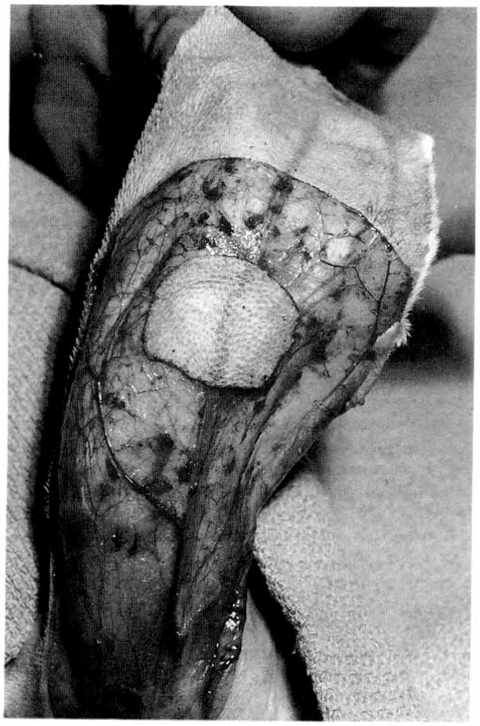

Fig 1. Dorsal surface of ear with perichondrium still adherent to auricular cartilage. Paddle of skin is maintained to monitor flap viability in neck.

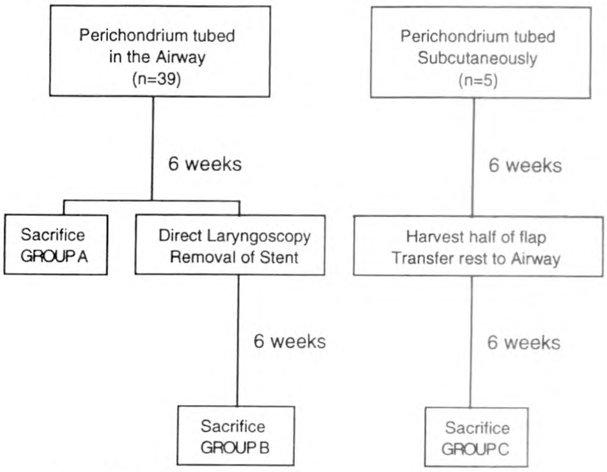
Perichondrium tubed in the Airway (n=39)
Perichondrium tubed Subcutaneously (n=5)
6 weeks
6 weeks
Sacrifice GROUP A
Direct Laryngoscopy Removal of Stent
Harvest half of flap Transfer rest to Airway
6 weeks
6 weeks
Sacrifice GROUP B
Sacrifice GROUP C

Fig 3. Flow diagram depicting experimental design.

neocartilage generated has the ability to provide adequate airway support.

MATERIALS AND METHODS

Animal Model. The New Zealand White rabbit was chosen as our animal model because it offers a large area of readily accessible auricular perichondrium with an identifiable vascular pedicle (Fig 1). This model permits transfer of dorsal auricular perichondrium and skin to the neck through a tension-free arc of rotation based on the dorsal auricular vascular pedicle. Adult rabbits of both sexes weighing 2.5 to 3.5 kg were used in the study.

Experimental Design. After anesthesia with xylazine hydrochloride (10 mg/kg intramuscularly [IM]) and ketamine hydrochloride (50 mg/kg IM), and administration of chloramphenicol sodium succinate (50 mg/kg IM), the ears and neck of the animal were shaved, prepared with Betadine, and draped in an aseptic fashion. A perichondrocutaneous flap was harvested from the dorsal surface of the auricle as previously described by Hartig et al[1] (Fig 2). The flap was passed through a subcutaneous tunnel connecting the root of the auricle to a midline neck incision. At this point, the reconstruction of the trachea was approached as either a single-stage or as a two-stage procedure (Fig 3).

One-Stage Reconstruction (Groups A and B). A two-ring segment of the cervical trachea was excised with the posterior tracheal membrane left intact to create a three-quarter circumferential (270°) defect. Prior attempts at creating a complete circumferential

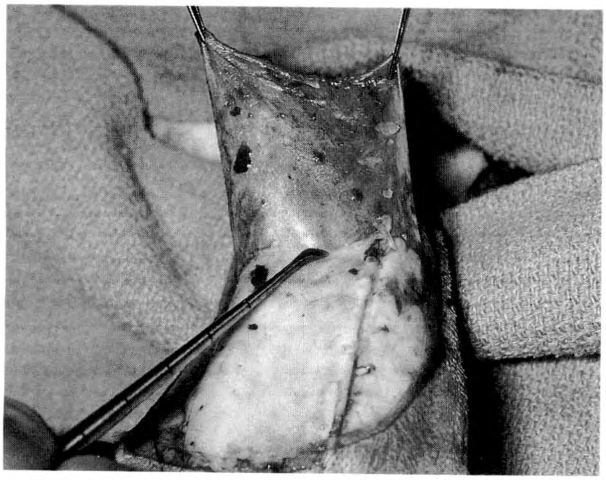

Fig 2. Perichondrocutaneous flap being elevated to root of auricle.

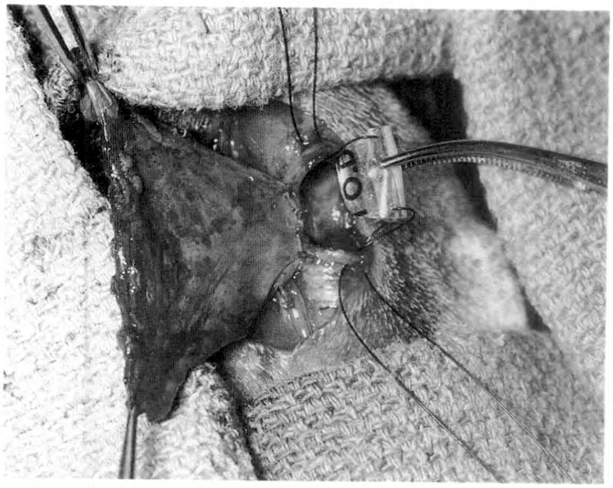

Fig 4. Tracheal stent being secured in airway with Prolene suture. Perichondrial flap is sutured to one side of tracheal defect.

defect were unsuccessful because of difficulty securing the stent to the cut tracheal edges and subsequent tracheal instability. A 1- to 1.2-cm-long stent was fashioned from a 4-mm–internal diameter Murphy endotracheal tube (Portex Blue Line tracheal tube) as described by Albert et al.[3] The stent was modified to the shape of a three-quarter tube, with the posterior tracheal membrane left unstented in order to minimize the tension on the repair site and to allow for mucociliary clearance, which would be significantly impaired with circumferential stenting of the lumen. Two simple sutures of 4.0 Prolene were placed to secure the stent anteriorly to the superior and inferior tracheal margins (Fig 4). With the perichondrium facing the stent, the flap was tubed around the stent and sutured to the margins of the tracheal defect with interrupted 5.0 Dexon to produce an airtight seal. The auricular skin paddle (Fig 1) was incorporated to the neck wound by approximating it to the edges of the neck incision with interrupted sutures of 4.0 chromic gut. This skin paddle was used for monitoring flap viability during the course of the experiment.

Immediately postoperatively the animals (n = 39) were randomized into one of two groups. Group A animals (n = 19) were painlessly sacrificed at 6 weeks following the reconstruction. The airways were harvested and fixed in formalin in preparation for histologic analysis. Group B animals (n = 20) were cared for in an identical fashion for the initial 6 weeks of the experiment. At 6 weeks, these animals underwent endoscopic removal of the stent under general anesthesia. Each animal in group B received a single preoperative dose of hydrocortisone sodium succinate (5 mg/kg IM). Following stent removal, the airway was irrigated with 2 mL of 1:100,000 racemic epinephrine and thoroughly suctioned. Any visible granulation tissue was debrided with a cup forceps. Animals were maintained for an additional 6 weeks prior to sacrifice.

Postoperative care and diet were identical for all animals for the duration of the study. Animals of either group that demonstrated signs of airway distress underwent direct laryngoscopy under general anesthesia with xylazine and ketamine. The airways were irrigated with saline and thoroughly suctioned, and any visible granulation tissue was removed.

Two-Stage Reconstruction (Group C). Group C consisted of 5 animals. The goal of this experiment was to prefabricate a rigid tube of cartilage from vascularized perichondrium for tracheal reconstruction to be performed at a second stage. The vascularized flap of auricular perichondrium was transferred to the neck in a manner identical to that in groups A and B. The perichondrium was then wrapped around a 3-cm section of endotracheal tube identical to the type, as described above, used to fashion the stent. The flap was tubed with the perichondrium facing the tube and the skin paddle facing anteriorly. The flap was sutured to itself around the tube by means of 5.0 Dexon and was buried in a paratracheal pocket. Two sutures of 3.0 Prolene were used to fix the tubed flap to the underlying strap muscles to avoid lateralization of the flap. The skin paddle of the flap was sutured to the edges of the neck skin in closure of the wound. Postoperative care and diet were identical to those of animals in groups A and B.

At 6 weeks the animals were returned to the operating room for exploration and assessment of cartilage formation by the perichondrial flap. There was uniform failure of the tubed flaps to provide rigid support, leading us to abandon this technique for planned reconstruction of a circumferential tracheal defect. At this time a 1- to 1.5-cm segment of perichondrium was harvested from one end of the tubed flap for histologic analysis, with care taken not to injure the vascular pedicle. The remainder of the flap, still attached to its vascular pedicle, was used to repair a 10- to 12-mm^2 triangular defect created in the cricothyroid membrane. The purpose of this experiment was to assess whether these perichondrial flaps, which had failed to generate a significant amount of cartilage subcutaneously around the tube, had the capacity to do so when transferred to the airway. The wound was closed in a similar fashion and animals were maintained for an additional 6 weeks prior to sacrifice.

Complications. There was 1 intraoperative death secondary to the general anesthetic. There were no deaths or complications in group C. None of the animals in any of the three groups demonstrated signs of vascular compromise of the flap as judged by the appearance of the auricular skin paddle in the neck.

Group A had 4 deaths, 2 occurring at 3 weeks and 2 at 4 weeks following airway reconstruction. In 1 animal the cause of death was unrelated to the airway. Necropsy of the other 3 animals demonstrated moderate granulation tissue formation at the edges of the stent, with mucous plugging of the stent. There was 1 immediate postoperative air leak, which was successfully treated with a pressure dressing. There were 3 auricular hematomas, which were treated with incision and drainage. One auricular wound infection was treated with debridement and topical silver sulfadiazine.

Group B had 3 deaths, all occurring at 4 weeks following airway reconstruction. One death was unrelated to the airway. Two deaths were secondary to mucous plugging of the stent, with granulation tissue

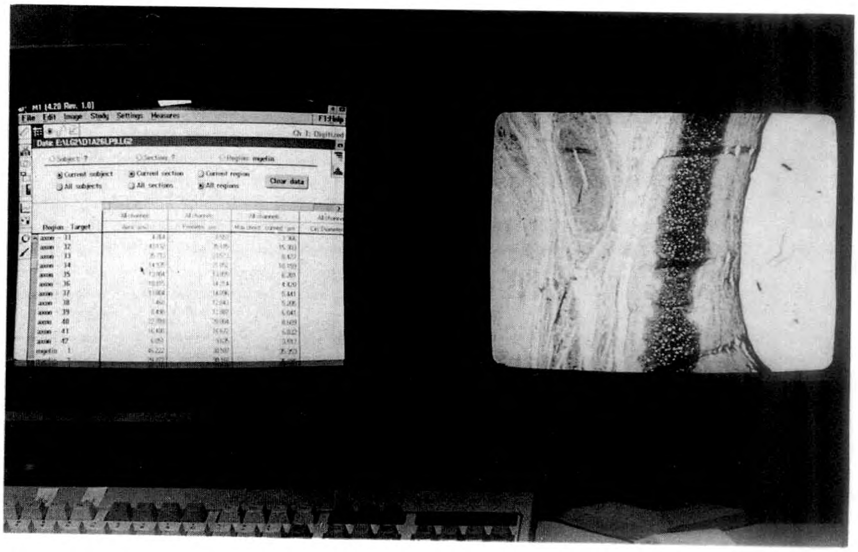

Fig 5. Image analysis apparatus shown with neocartilage specimen being quantified on computer screen.

present at the margins of the repair. There were two air leaks, managed successfully with pressure dressings. Two auricular hematomas and 1 auricular wound infection were treated as described above. In the group B animals that underwent stent removal at 6 weeks (n = 17) there were 5 deaths. Two of these deaths were within the first day following removal of the stent. The other 3 deaths in this group occurred at a period of 2 to 3 weeks following removal of the stent. All 5 airways had an appropriate neocartilage thickness, but there was considerable granulation tissue formation and scarring resulting in significant airway stenosis (>75% of lumen) in 3 of the 5. These findings were confirmed histologically.

Data Analysis. Specimens were formalin-fixed, embedded in paraffin, and sectioned in 5-μm-thick sections with a microtome. Twelve to 15 slides were prepared from each specimen by taking sections at 0.1-mm intervals along the entire length of the reconstructed airway. The slides were stained with hematoxylin and eosin. Slides were reviewed by the first author in a blinded fashion. Light microscopic images were digitized onto a computer equipped with image analysis software (MCID-M1, Version 4.20 Rev. 1.0; Imaging Research Inc, Saint Catharines, Canada). With the image on the computer screen, areas of cartilage were easily distinguishable within the specimen (Fig 5). A total of 150 to 200 readings were taken from each airway specimen and combined to obtain the average thickness of each individual specimen.

RESULTS

One-Stage Reconstruction. Group A had a mean cartilage thickness of 0.425 ± 0.083 mm. There were 4 deaths prior to 6 weeks, resulting in a 79% survival rate. By excluding early mortalities, a slightly higher mean cartilage thickness of 0.441 ± 0.082 mm at 6 weeks is derived (p = not significant).

Group B animals had a mean cartilage thickness of 0.530 ± 0.100 mm. There were 3 deaths in this group prior to stent removal at 6 weeks, resulting in an 85% survival rate. Of the animals that underwent stent removal (n = 17) there were 5 additional deaths over the course of the following 6 weeks, resulting in a survival rate of 71%. The mean cartilage thickness for group B animals sacrificed at 12 weeks following reconstruction (n = 11) was 0.559 ± 0.112 mm. One randomly selected animal from group B was maintained for an additional 12 weeks. The cartilage thickness of the reconstructed trachea of this animal at 24 weeks was 0.454 mm. All perichondrial flaps tubed in the airway generated neocartilage that histologically resembled mature cartilage (Fig 6).

Comparison of the two groups revealed a significant difference ($p < .005$, *t*-test) in neochondrogenesis between the group A animals alive at 6 weeks and the group B animals alive at 12 weeks. By adding the thickness data from the airways of animals that died prior to the planned intervals, it is observed that the majority of cartilage growth from vascularized perichondrium occurs in the initial 3 to 4 weeks (Fig 7). Chondrogenesis, however, continues, albeit at a slower rate, beyond 6 weeks.

Two-Stage Reconstruction. Group C animals underwent exploration of the subcutaneously tubed flap at 6 weeks, at which time half the flap was harvested and the remaining half was transferred to the airway. Histologic analysis of the segments of subcutaneously tubed vascularized perichondrium harvested at 6 weeks from group C animals revealed a mean cartilage thickness of 0.099 ± 0.076 mm. The mean cartilage thickness of the flaps 6 weeks after transfer to the airway was 0.364 ± 0.192 mm. A significant

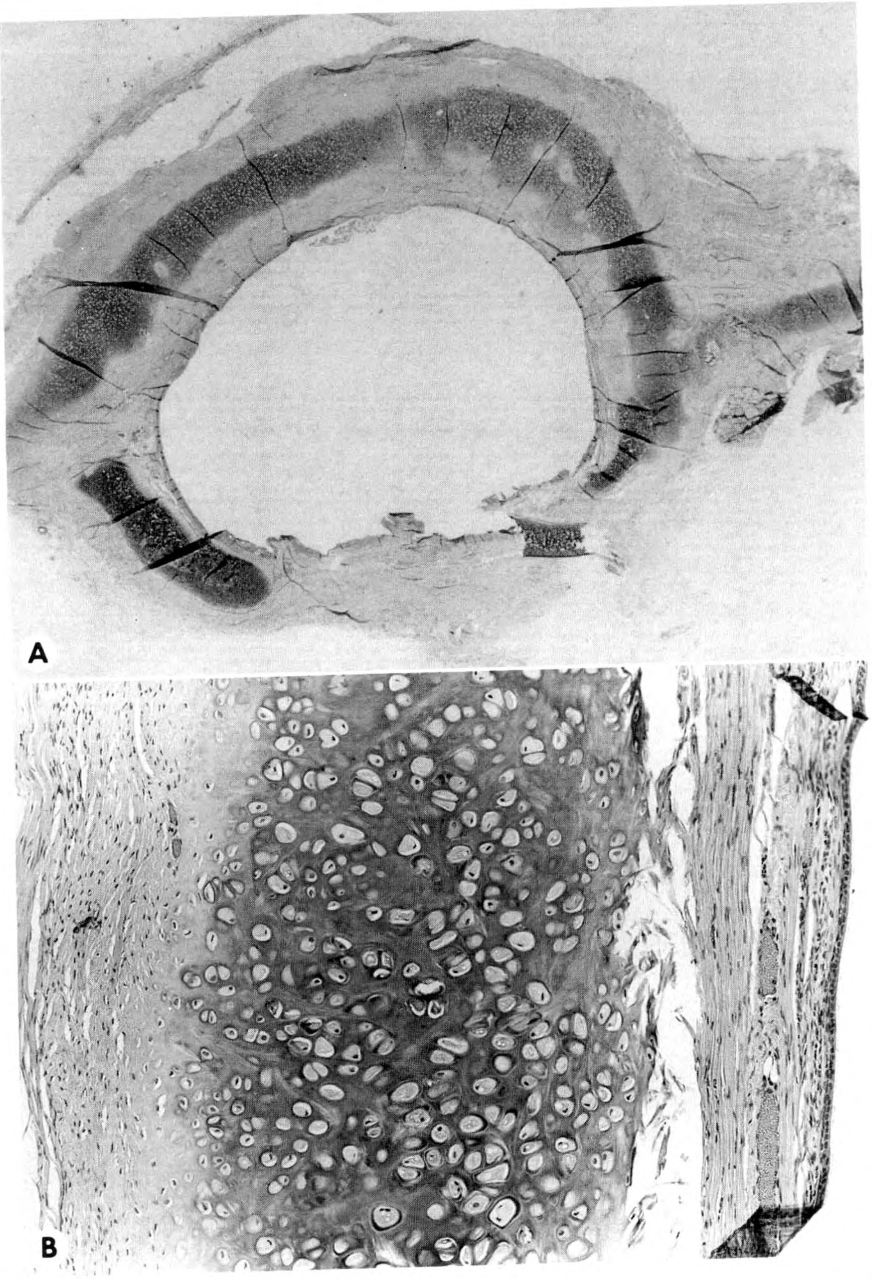

Fig 6. A) Transverse section through reconstructed trachea showing dark-staining neocartilage spanning airway and continuing into pedicle. B) More detailed image showing microscopic appearance of neocartilage, which greatly resembles mature cartilage.

increase in chondrogenesis ($p < .05$) was observed following transfer to the airway.

DISCUSSION

The most significant finding in this study was that vascularized perichondrium was successfully used for reconstruction of a near-circumferential tracheal defect. The integrity of the reconstructed airways was evaluated at 6 weeks, with 71% of the animals surviving an additional 6 weeks following stent removal. Histologic analysis of the early mortalities demonstrates that the cause of airway compromise was not the lack of chondrogenesis, but granulation tissue formation, scarring, and stenosis. It is difficult to draw direct conclusions from the above survival rate, since the animals did not have a tracheostomy. Airway bypass might have prevented those deaths that were due to mucous plugging of the stent or mucosal edema following stent removal and instrumentation.

The next finding of this study is that a significant proportion of chondrogenesis by vascularized auricular perichondrium in the airway takes place in the initial 3 to 4 weeks. Nonetheless, there appeared to be a modest though significant increase in the amount of cartilage formed at 12 weeks as compared to 6 weeks. Although cartilage thickness continued to increase beyond 6 weeks, it did so at a much slower rate than in the initial 6 weeks and then appeared to level off. The majority of complications noted in this study were secondary to the presence of an airway stent. It

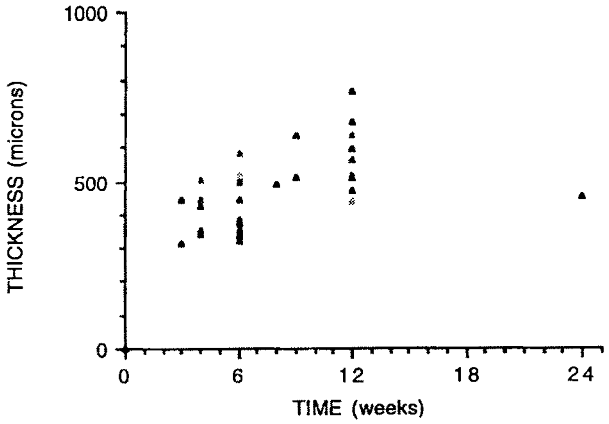

Fig 7. Plot of cartilage thickness over time, combining animals from groups A and B. Thickness curve = (89.7)(t) − (3.2)(t^2), where t = time in weeks ($p < .0005$).

has been previously observed in a normal rabbit trachea that a stent identical to the one used in the present study was capable of producing ischemic changes and resulted in an inflammatory process.[3] Since most of the chondrogenesis occurs in the initial 3 weeks, it may be possible to substantially shorten the required period of intraluminal stenting. Furthermore, it is imperative that the long-term growth potential of all vascularized perichondrial or periosteal grafts being considered for airway reconstruction be evaluated. Specifically with such grafts, the possibility of airway obliteration by incessant growth of cartilage or bone should be examined. The present study suggests a leveling off of cartilage thickness by 24 weeks (Fig 7), but a longer evaluation at 1 to 2 years would be required to confirm this observation.

Our last finding is that vascularized perichondrium did not appear to generate significant amounts of cartilage when tubed and buried subcutaneously. These results confirm the prior findings[4] that untubed free and vascularized auricular perichondria both generate significantly less cartilage subcutaneously than they do in the airway. Kon and van den Hooff[5] found that free auricular perichondrium placed subcutaneously displayed poor chondrogenesis and failed to form a rigid tube around a silicone rod. A serendipitous discovery made in our study is that delayed transfer of perichondrium to the airway at 6 weeks can still serve as a potent stimulus for chondrogenesis. There was more than a threefold increase in cartilage formation over a 6-week period following such transfer. The mechanism by which exposure to the airway enhances the chondrogenicity of perichondrium is purely speculative, but possibilities include the influence of the bacterial flora, air turbulence, and differences in temperature. The other possibility is the existence of a suppressive action by the soft tissue environment on the growth of cartilage. The poor chondrogenicity achieved outside the airway indicates that a two-stage method of tracheal reconstruction using vascularized perichondrium does not appear to be practical in this model. However, this finding needs to be tested in other animal models by means of vascularized periosteal flaps.

In contrast, vascularized periosteum is capable of generating a substantial amount of bone in a sterile subcutaneous environment.[6-10] Krespi et al[10] created a rigid tube of bone by tubing a pedicled pleuroperiosteal flap in the chest wall. Takato et al[11] have also shown that vascularized tibial periosteum generates bone reliably as a pedicled flap.

Vascularized periosteum is a promising source of grafting tissue for airway reconstruction in humans. Periosteum may be harvested for free microvascular transfer to the neck from multiple donor sites, including the iliac fossa, distal humerus, and distal femur.[12] Successful free microvascular transfer of an iliac fossa musculoperiosteal flap for repair of a severely comminuted tibial fracture has been reported, where rigid bone formation was observed.[13] A vascularized tube of bone can be created at the donor site by tubing pedicled periosteum around a mold. After several weeks, reconstruction of the trachea can be accomplished by microvascular transfer of the pedicled tube to the neck. A major advantage of this approach is that it omits the need for stenting. We are currently evaluating a larger animal model to develop and test potential vascularized periosteal flaps for airway reconstruction.

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LANGUAGE DEVELOPMENT IN COCHLEAR IMPLANTED CHILDREN

The International Conference on Language Development in Cochlear Implanted Children will be held December 8-9, 1996, in Lyon, France. For more information, contact Prof A. H. Morgon, Hopital Edouard Herriot, pavillon U, place d'Arsonval, 69003 Lyon, France; telephone (33) 72.11.05.35; fax (33) 72.11.05.34.

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FUNCTIONAL ENDOSCOPIC SINUS SURGERY: BASIC AND ADVANCED TECHNIQUES

The course Functional Endoscopic Sinus Surgery: Basic and Advanced Techniques will be held in Graz, Austria. The English course will be held July 11-13, 1996, and the German course September 5-7, 1996. For further information, contact Prof H. Stammberger, MD, ENT Department, University Hospital, Auenbruggerplatz 20, A-8036 Graz, Austria; fax ++43 316 385 3425.

Ann Otol Rhinol Laryngol 105:1996

LARYNGOTRACHEAL RECONSTRUCTION USING A VITALLIUM ALLOY MINIPLATE

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When stenosis of the larynx and trachea involves loss of anterior support, this is usually corrected by an autograft of costochondral cartilage or of hyoid bone anchored with suture material. This paper describes an alternative technique employing a Vitallium alloy miniplate placed anterior to the airway as a means for providing support. This is placed over a fascial or auricular cartilage graft. Together, they provide a smooth scaffold for mucosal migration. Thirteen patients were treated at Indiana University Medical Center between 1991 and 1993 by means of this technique. Ten of the 13 patients (77%) achieved an adequate airway to allow decannulation. There have been no significant complications related to the use of the miniplate, and specifically, there have been no instances of infection or extrusion. It has been unnecessary to remove any of the miniplates. The Vitallium alloy miniplate offers unique advantages in laryngotracheal reconstruction in that it not only accurately approximates tissues, but it also provides external support to the airway.

KEY WORDS — airway, graft, laryngotracheal reconstruction, miniplate, stenosis, Vitallium.

INTRODUCTION

Correction of stenoses of the subglottis and upper trachea remains a challenging surgical problem. Numerous techniques have been described. Most involve an anterior opening of the airway with insertion of graft material to provide support and to maintain the airway in an expanded configuration.

PATIENTS

Since 1991, 13 patients with subglottic and/or upper tracheal stenosis have been treated with an anterior midline split of the airway that is maintained by utilizing an auricular cartilage perichondrial graft or fascia reinforced with a Vitallium miniplate.

The causes of the stenoses were diverse and included intubation trauma in 8 patients, tracheotomy in 2 patients, destruction by neoplasm in 1 patient, sequelae of vertical hemilaryngectomy in 1 patient, and thyroiditis with tracheal involvement and compression in 1 patient. There were 10 females and 3 males. The age range was from 14 months to 88 years, with a median of 51 years. There were 3 teenagers and 2 patients less than 10 years of age. (One was 14 months old.) Three patients were 79 years of age or older. The median length of follow-up was 32 months, the mean 31 months, and the range 18 to 51 months.

TECHNIQUE

A 7-cm incision is made in a skin crease approximately one fingerbreadth above the tracheal stoma. Skin flaps are elevated superiorly and inferiorly in the equivalent of a subplatysmal plane. A short vertical limb is dropped down to the tracheal stoma, as it is felt critical to gain adequate exposure of this area to assess pathologic changes and correct them during the surgical procedure. Laryngotracheal fissure is performed in the midline from the tracheal stoma up to, and often through, the anterior commissure (Fig 1).

The mucosa and scar tissue of the airway, thus exposed, are injected with 1% Xylocaine with 1:100,000 epinephrine, providing the necessary hemostasis for precise, conservative resection of scar tissue with maximum preservation of epithelium. Scar

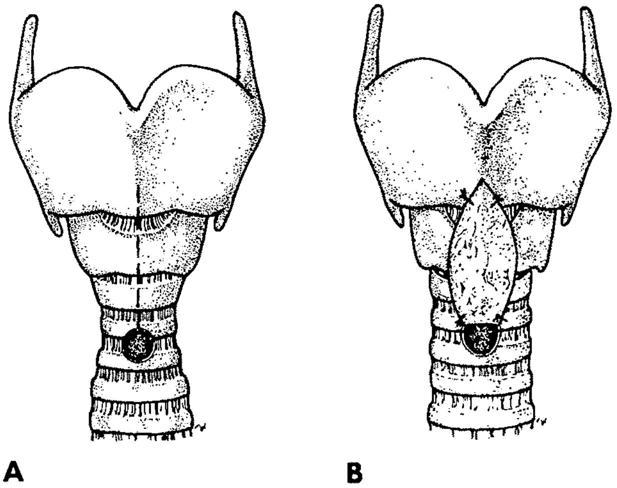

Fig 1. Technique of exposure of interior of airway. A) Laryngotracheal fissure from tracheal stoma to just below anterior commissure. B) Airway retracted laterally, expanding lumen and creating gap to be bridged by miniplate and fascia or auricular cartilage graft.

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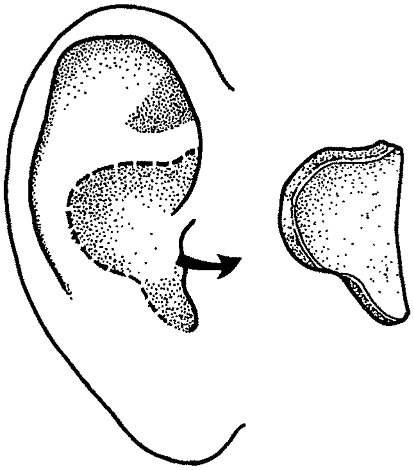

Fig 2. Auricular cartilage graft from concha harvested via incision just inside antihelix. Perichondrium is left on concave surface.

tissue is resected from the posterior commissure and interarytenoid area when appropriate. A posterior midline division of the cricoid cartilage can be performed at this time.

The auricular cartilage graft is harvested by making an incision just inside the antihelix of the external ear. The lateral skin is elevated from the conchal cartilage.

Perichondrium is left attached to the concave surface of the conchal cartilage, and often to the convex side. Closure of the donor site includes a quilting suture of 3-0 chromic passed back and forth to eliminate dead space. An approximately 2.5 × 2.5-cm graft is thus obtained (Fig 2). This can be shaped into the appropriate ellipse to augment the anterior tracheal wall.

An appropriate-size Cotton-Lorenz Teflon stent (10- to 12-mm diameter in adults) is selected that allows reapproximation of the anterior commissure without undue tension. The superior aspect of the stent should be level with the false vocal cords and arytenoid cartilages. The Teflon stent is cut to an appropriate length so that it extends to the superior wall of the tracheotomy tube. The lower end of the stent is cut on a bevel to conform to the shape of the superior aspect of the tracheotomy tube outer cannula and is filed to eliminate any rough edges.

When the anterior commissure has been divided, the thyroid cartilage is approximated with 4-0 polydioxanone sutures, with care taken so that the anterior portion of each true vocal cord is at exactly the same level.

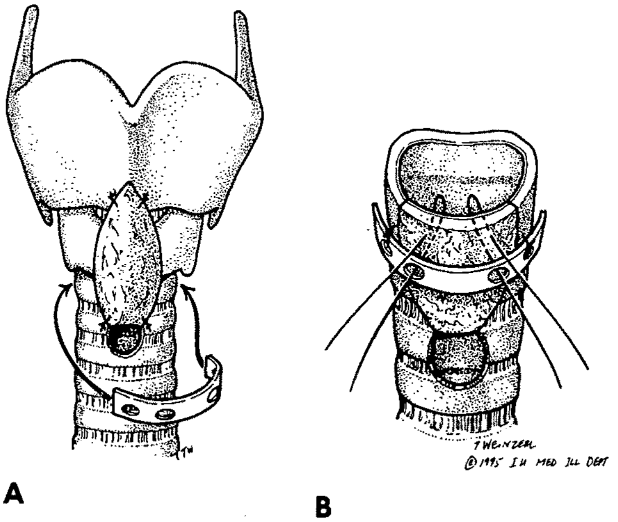

Fig 3. Stabilization of graft to expand airway. A) Cartilage-perichondrium graft is sutured into gap created by airway expansion. B) Vitallium miniplate is sutured laterally to tracheal wall and medially, so that it suspends and provides external support to graft.

The auricular cartilage graft is cut to its appropriate size and shape (most commonly 2.5 × 2 cm) and positioned with the concave surface and attached perichondrium facing inward toward the lumen. The cartilage graft is fixed to the adjacent tracheal or thyroid cartilage, employing approximately four 4-0 polydioxanone sutures. Often, the lower end of the graft extends to the tracheal stoma. Usually, one four-hole, 29-mm noncompression Vitallium alloy miniplate is bent to the appropriate shape that recreates the desired anterior curve of the expanded trachea. This is fixed with 4-0 polydioxanone sutures to the trachea laterally. Subsequently, 4-0 mattress sutures are placed through the central holes of the miniplate, and then through the dome of the cartilage graft, to act as an external "rib," simulating the support system of an umbrella tent (Fig 3). When fascia is used as the anterior graft material, it is harvested from a sternocleidomastoid muscle, or a flap is formed from the fascia overlying a strap muscle. This is interposed between the tracheal lumen and an external miniplate. More than one miniplate can be used for longer stenoses. Two miniplates were used in 1 patient in this series, and the patient was successfully decannulated. The miniplate can be placed within 1 cm of the tracheal stoma if support is required in this area. The skin is closed and a Jackson tracheotomy tube, with an inner cannula incorporating an anesthesia adapter, is inserted. A standard Jackson inner cannula is substituted in the recovery room.

RESULTS

Ten of the 13 patients were decannulated. In 7 patients an auricular cartilage graft plus a Vitallium miniplate was employed, and 6 were decannulated. In 5 patients a miniplate over fascia was utilized, and in another a miniplate was placed over a malacic

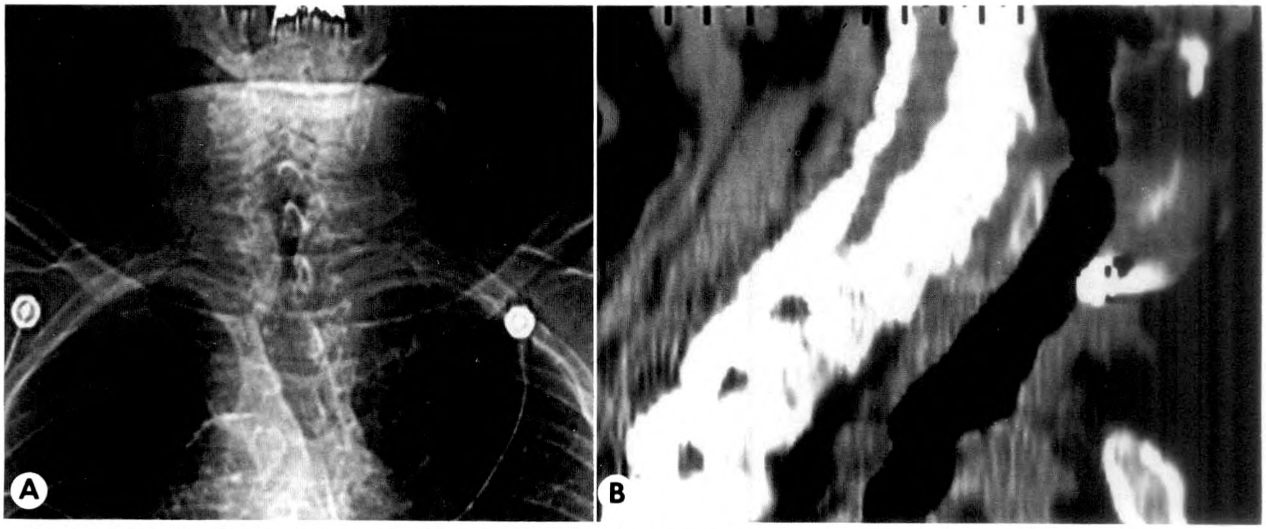

Fig 4. Computed tomograms of 88-year-old man with acquired stenosis above previous tracheotomy. A) Preoperative. B) Spiral scan of upper airway after surgical correction of stenosis employing Vitallium miniplate.

anterior tracheal wall with suprastomal collapse. Four of these latter patients were decannulated. The stent was left in place for 3 to 6 weeks, with a median of 4 weeks. The length of time to decannulation after stent removal, in successful cases, was 4 to 12 weeks, with a median of 5 weeks.

Six patients had undergone one or more previous open procedures, employing rib cartilage or hyoid bone grafts, that had not been successful in allowing decannulation. Only 3 of these 6 patients were decannulated after laryngotracheoplasty employing auricular cartilage or fascia supported by a Vitallium plate. One of these patients was a 12-year-old boy with subglottic stenosis induced by prolonged intubation for bronchopulmonary dysplasia. Five open procedures and numerous endoscopic laser procedures had been unsuccessfully performed to provide an adequate airway. Auricular cartilage was used as the anterior graft material. Each procedure was followed by exuberant granulation tissue and a progressive glottic, subglottic, and tracheal stenosis. Evaluation for, and therapy directed toward, suspected gastroesophageal reflux, prolonged stenting, and creation of a subglottic and tracheal trough[1] were without success.

An 8-year-old girl with a similar cause for her stenosis underwent four open procedures and several endoscopic laser procedures without obtaining an adequate airway. Fascia was used as the anterior graft material.

The third patient was a 79-year-old woman who sustained bilateral vocal cord paralysis as a complication of parathyroidectomy. She had two attempts at arytenoidectomy that were complicated by glottic posterior commissure and subglottic stenosis. This stenosis recurred after laryngotracheoplasty with fascia supported by a miniplate.

Among the patients who were successfully decannulated there were several complications. In 3, tracheocutaneous fistulas persisted and all were successfully closed by simple excision of the mature tract with subsequent healing by secondary intention. An 88-year-old man had persistent copious tracheobronchial secretions requiring admission on two occasions, but also had adequate caliber of the airway for respiration without stridor or evidence of obstruction (Fig 4). There were no instances of infection of the miniplate requiring its removal, and no instances of extrusion of the plate. This included several patients in whom the miniplate was fixed just superior to the tracheal stoma to provide suprastomal support of the airway.

DISCUSSION

Open surgical repair of subglottic and/or upper tracheal stenosis that is too severe to permit endoscopic correction can be accomplished by anterior and/or posterior vertical incision of the airway, allowing the airway to open or expand. This expansion is usually maintained by inserting some sort of autogenous material in the space thus created.[2-7] With more limited lesions, anterior incision of the airway and stenting may provide adequate expansion.[8,9]

Conchal cartilage is an excellent graft material for expansion of the airway for several reasons.[4,5,10] The external ear can be easily included in the surgical field, and there is essentially no long-term donor site morbidity. Conchal cartilage has a natural concavity that reiterates the shape of the anterior tracheal wall. The perichondrial layer is thin and smooth, providing an excellent surface for epithelial migration from adjacent respiratory mucosa. Auricular cartilage is thin in comparison to rib cartilage and therefore has less inherent rigidity. However, this rigidity is provided by the Vitallium miniplate. Moreover, the pliability allows the surgeon to shape the auricular cartilage as best serves the reconstruction.

Alloplastic materials, including miniplates, have been used for laryngeal reapproximation after trauma and for external support of the airway after reconstruction following resection of stenosis.[11,12] They offer an advantage over suture alone, in that accurate approximation is accomplished along with provision of support.

The cartilage graft and miniplate can be placed, respectively, at and close to the superior aspect of the tracheal stoma, providing support in this area when required. Suprastomal collapse is a not-infrequent cause of failure to decannulate a patient with airway stenosis after surgical correction.

Despite placement close to the tracheal stoma, we have experienced no infection or extrusion of the miniplate. As noted, this was with a median length of follow-up of 32 months. The miniplate can be palpated beneath thin skin postoperatively, but we have had no requests to remove the plate.

We anticipate, in the near future, the availability of miniplates made of polylactic and polyglycolic acid so that eventually resorption of the plate will occur.[13] We have performed two laryngotracheal reconstructions using such resorbable plates. The results are encouraging, but the number of patients and the length of follow-up need to be expanded.

In 6 patients in our series, an auricular cartilage graft was not required and the miniplate was placed external to a fascial graft or to a malacic anterior tracheal wall to achieve a patent and stable airway.

Allowing for tracheal growth is a consideration with children. Since the miniplate is fixed to the graft and trachea with resorbable suture, it will maintain its position anterior to the trachea, but is not permanently bonded to a particular point on the tracheal wall. Therefore, the movement of the tracheal wall relative to the plate that occurs with growth should not be impeded. The 14-month-old child in this series has had no recurrence of stridor despite the elapse of 2½ years since the employment of the miniplate.

SUMMARY

We have described a technique of open surgical correction for subglottic and/or upper tracheal stenosis utilizing a Vitallium miniplate to provide external support. In most cases, expansion of the airway is accomplished with concomitant use of an auricular cartilage graft. The unique advantages of auricular cartilage for airway reconstruction are described. This technique allowed decannulation without airway obstruction in 10 of 13 patients. Two of the 3 failures had had multiple prior surgical procedures and tended to form exuberant granulation tissue.

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ADHERENCE OF NONTYPEABLE *HAEMOPHILUS INFLUENZAE* TO RESPIRATORY EPITHELIUM OF OTITIS-PRONE AND NORMAL CHILDREN

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Three hundred six children were enrolled at birth in a prospective study of otitis media and followed up for 2 years. Adherence of nontypeable *Haemophilus influenzae* to buccal epithelial cells was compared between otitis-prone children and age- and sex-matched normal controls at birth, 1 year, and 2 years. The mean ± SD/median percent adherence was similar for the two groups at birth (1.6 ± 2.3/1.0 versus 1.2 ± 1.4/1.0; NS) and at 2 years (1.6 ± 1.7/1.5 versus 2.1 ± 2.1/1.5; NS). At 1 year of age the adherence rate for the otitis-prone group (2.4 ± 2.6/1.0) was statistically greater than that for the control group (1.0 ± 1.3/0.0; $p < .02$). Because this difference is probably clinically insignificant, other explanations must be sought for the increased colonization rates of nontypeable *H influenzae* observed in otitis-prone children.

KEY WORDS — bacterial adherence, nontypeable *Haemophilus influenzae*, otitis media.

INTRODUCTION

Nontypeable *Haemophilus influenzae* commonly colonizes the upper respiratory tract of children and has the potential to cause local disease such as otitis media and sinusitis. Children who are prone to recurrent episodes of otitis media are colonized repeatedly with nontypeable *H influenzae*.[1,2] Increased colonization may reflect increased exposure as observed in day-care centers and in families with siblings.[3-5] It is also possible that colonization represents different degrees of avidity between the organism and the cell. Porras et al[6] failed to demonstrate differences in adherence between strains of nontypeable *H influenzae* isolated from children with otitis media, suggesting that differences in adherence rates were independent of the organism. The present study was designed to determine whether a single strain of nontypeable *H influenzae* adhered differently to buccal epithelial cells isolated from otitis-prone children compared to normal children.

MATERIALS AND METHODS

General Design of Study. Children were enrolled in the study in the first month of life and followed up prospectively for 2 years. They were examined routinely at 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 21, and 24 months of age. At each visit, ear examinations were conducted with pneumatic otoscopy and tympanometry. Nasopharyngeal cultures were obtained at all scheduled visits. Buccal epithelial cells were collected at 1, 12, and 24 months. The number of ear infections and number of episodes of colonization with nontypeable *H influenzae* were documented. Adherence studies were performed with buccal cells from otitis-prone and normal children.

Acute otitis media was defined as the presence of fever, irritability, ear pulling, or ear pain in a child with a thickened, bulging, immobile eardrum and a flattened tympanogram. Children were defined as otitis-prone if they experienced four or more episodes in the first year of life or six or more episodes by 2 years of life. A new episode of otitis media was not diagnosed until all signs and symptoms of a previous episode had resolved.

Children without a history of otitis media and without nasopharyngeal colonization with nontypeable *H influenzae* were selected as controls and matched for age and sex with otitis-prone subjects.

Adherence Assay. Buccal cells were collected by rubbing two cotton-tipped swabs on both buccal surfaces. The swabs were agitated in Hanks' balanced salt solution (HBSS) with 0.1% gel and transported to the laboratory at room temperature. The cell suspension was centrifuged at 300*g* and washed in HBSS with 0.1% gel. The procedure was repeated three times before suspending the cells at a concentration of 2×10^4 cells per milliliter in minimal essential medium with 10% dimethyl sulfoxide. This preparation was frozen at −70°C until the assay was to be run.

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After thawing, more than 90% of the cells were viable.

Nontypeable *H influenzae* was passed on chocolate agar weekly and grown overnight in brain-heart infusion (BHI) broth supplemented with 10 µg/mL of nicotinate adenine dinucleotide and 10 µg/mL of hemin at 37°C in 5% carbon dioxide (CO_2). One milliliter of the bacterial suspension was transferred to fresh BHI broth with ^{3}H-thymidine (0.008 mCi/mL, 31 Ci mmol/L specific activity, Schwarz/Mann, Orangeburg, NY) that had been preincubated in 5% CO_2. The radioactive preparation was incubated at 37°C in 5% CO_2 until the organism reached mid-log phase growth — approximately 4 to 6 hours. The suspension was centrifuged at 2,000*g*, resuspended in HBSS with 0.1% gel, and centrifuged at 2,000*g*. The bacterial suspension was diluted in HBSS with 0.1% gel to obtain a concentration of 1×10^9 colony-forming units per milliliter.

Buccal cell suspension (0.5 mL) and bacterial suspension (0.5 mL) were mixed in a biovial and incubated at 37°C for 60 minutes on a rocker. A bacteria control was included in the assay. At completion of the incubation the suspension with the buccal cells was centrifuged at 30*g* for 10 minutes. The supernatant was decanted and replaced with fresh HBSS with 0.1% gel. This was repeated two more times. A control with buccal cells and bacteria was centrifuged once at 2,000*g* for 15 minutes to obtain the total isotopic content in each vial. After the final centrifugation and removal of supernatant, 0.3 mL of Solvable (Dupont NEN Research, Boston, Mass) and 2.7 mL of Aquasd-2 (Dupont NEN Research) were added and incubated overnight at 4°C. The preparation was mixed and counted in a beta scintillation counter. Each preparation was run in duplicate or triplicate. Cells from otitis-prone individuals, controls, and a single individual in the laboratory who served as an internal control were tested concurrently. The laboratory donor was included in each run to ensure reproducibility of the assay. Adherence was calculated according to the formula

$$\frac{\text{counts/minute test sample} - \text{counts/minute bacteria}}{\text{counts/minute total}} \times 100 = \%\ \text{adherence}$$

Statistics. Each assay was reviewed to be certain that the adherence value of the internal control remained within 2 SD of the mean of the internal control for all runs; assays that exceeded this limit were discarded from the tabulation. Adherence values were logarithmically transformed to better represent a normal distribution before we performed nonparametric statistical testing on the age-matched samples. Differences in mean log adherence values between otitis-prone children and their controls were compared by Mann-Whitney rank sum test. Colonization rates in otitis-prone children were correlated with adherence by Spearman's correlation coefficient as a means of determining whether the in vitro test reflected in vivo adherence. The effect of breast feeding on adherence was determined by comparing differences in adherence rates in breast-fed and bottle-fed infants by Mann-Whitney rank sum test.

RESULTS

Three hundred six children were enrolled in the study. For purposes of the present analysis, buccal cells were collected in 40 of the otitis-prone children and compared with normal controls similarly matched for age and other identifying characteristics. Forty children were classified as otitis-prone: 26 within the first year and 14 by 2 years. Fifty-six children (70%) were breast-feeding at enrollment. By 1 year, the number of breast-fed children declined to 10 (12.5%), and none were breast-feeding at 2 years. No differences in the level of adherence between breast-fed and bottle-fed infants was found at the 1-month determination (p = not significant [NS]), nor at the 1-year determination (p = NS) and, therefore, method of feeding was not considered in subsequent analyses.

An internal control was tested in each assay to assess day-to-day variation in the assay. The mean ± SD and median adherence of the internal control were 0.7 ± 1.0% and 0%, respectively. Scatterplots of log adherence values revealed that two assay values were detected in which the internal control exceeded 2 SD above the mean. Summary statistics were performed with and without the two outliers, but the variability did not change results significantly. Results are, therefore, presented with the two outliers excluded.

Mean adherence rates in cells collected at birth (mean ± SD 1.4% ± 1.9%, median 1.0%) were similar to the rates observed at 1 year (mean ± SD 1.7% ± 2.2%, median 1.0%) and at 2 years (mean ± SD 1.9% ± 1.9%, median 1.5%) for the 80 children studied. Comparison of mean adherence rates between otitis-prone children (mean ± SD 1.6% ± 2.2%, median 1.0%) compared to normal controls at birth (mean ± SD, 1.2% ± 1.4%, median 1.0%, p = NS) and at 2 years of age (mean ± SD 1.6% ± 1.7%, median 1.5%) versus normal controls (mean ± SD 2.1% ± 2.1%, median 1.5%, p = NS) revealed some variability, but the results were not significant (see Table). However, at 1 year of age, mean adherence in the otitis-prone group (mean ± SD 2.4% ± 2.6%, median 1.0%) significantly exceeded adherence in the normal con-

COMPARISON OF ADHERENCE RATES BETWEEN NORMAL CHILDREN AND OTITIS-PRONE CHILDREN AT BIRTH, ONE YEAR, AND TWO YEARS OF AGE

	Mean ± SD/Median Percent Adherence		
Age	*Normal Control*	*Otitis-Prone*	*p*
Birth (39/39*)	1.2 ± 1.4/1.0	1.6 ± 2.3/1.0	.60
1 year (26/26*)	1.0 ± 1.3/0.0	2.4 ± 2.6/1.0	<.02
2 years (14/14*)	2.1 ± 2.1/1.5	1.6 ± 1.7/1.5	.64

*Normal control children/otitis-prone children.

trol group (mean ± SD 1.0% ± 1.3%, median 0%, $p < .02$; see Table). Given the limited sample, this difference is minimal and probably not clinically relevant.

Colonization with nontypeable *H influenzae* was common among the otitis-prone group. By 1 year of age, 52.5% of these children had been colonized. By 2 years of age, the proportion of children colonized increased to 67.5%. In order to determine the relationship between adherence rates observed in vitro and the frequency of colonization observed in vivo, we next performed Spearman's correlation coefficient for cells collected at 1 year and 2 years, and found no significant relationship (1 year $r = .04$, $p =$ NS; 2 years $r = .01$, $p =$ NS).

DISCUSSION

The present study examined the adherence of nontypeable *H influenzae* to buccal epithelial cells collected from otitis-prone children and control children (no history of otitis media and no nasopharyngeal colonization with nontypeable *H influenzae*). Both groups were part of a large prospective study in which enrollment took place in the first month of life. Each group comprised 40 children. Adherence was determined at entry into the study and at 1 year or 2 years of age.

Numerous studies have examined adherence of *H influenzae* to various cells in vitro. The majority of studies have demonstrated that nontypeable strains of *H influenzae* adhere better than encapsulated strains.[7-11] Fimbriae are an important mechanism for attachment of both types of organisms.[12-17] A fimbrin protein consisting of 338 amino acids has been identified as the part of fimbriae that adheres to the cell surface.[17] The structure of the receptor for the fimbriae on human cells is a sialyl-lactosylceramide.[15] *Haemophilus influenzae* may also adhere to cells via surface proteins other than fimbriae.[18-23] Two high–molecular weight proteins, in particular, act as adhesins.[20,21] These proteins are morphologically similar to the filamentous hemagglutinin of *Bordetella pertussis*.[20,21] The proteins recognize a glycoprotein receptor on the cell surface.[23] The degree of sulfation and the particular carbohydrate moiety contained in the receptor greatly influence adherence.[22]

Although in vitro studies that utilize isolated cells are able to establish mechanisms of attachment in the artificial environment, the mechanism(s) may not apply to the in vivo setting. As observed in the present study, no relationship existed between the degree of adherence in the assay and the frequency of nasopharyngeal colonization with nontypeable *H influenzae*. It is possible that adherence of *H influenzae* to buccal epithelial cells is not a good model of adherence in the nasopharynx. A recent study examined adherence in a nasopharyngeal organ culture system and determined that mucus contained components that specifically bound *H influenzae*.[24] In our own laboratory, *H influenzae* was not observed in mucosal biopsy specimens despite high numbers of organisms in simultaneously collected nasopharyngeal secretions.[25] Finally, we have recently observed adherence of several outer membrane proteins of nontypeable *H influenzae* to purified nasopharyngeal mucin, further suggesting that nontypeable *H influenzae* attaches to the mucus layer over the epithelium. It is reasonable to speculate that *H influenzae* normally attaches to the mucus layer during healthy periods; however, during disease, the organism invades deeper structures after attaching to the cell.

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BELL'S PALSY TREATMENT WITH ACYCLOVIR AND PREDNISONE COMPARED WITH PREDNISONE ALONE: A DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL

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In a double-blind study, we compared the final outcome of 99 Bell's palsy patients treated with either acyclovir-prednisone (53 patients) or placebo-prednisone (46 patients). For patients receiving acyclovir, the dosage was 2,000 mg (400 mg 5 times daily) for 10 days. Electrical tests included electroneurography and the maximal stimulation test. Univariate comparisons of outcome and electrical tests between the two groups were made with χ^2 analysis, Fisher's exact test, and *t*-tests. The outcome in acyclovir-prednisone–treated patients was superior to that in placebo-prednisone–treated patients. Treatment with acyclovir-prednisone was statistically more effective in returning volitional muscle motion (recovery profile of 10; $p = .02$) and in preventing partial nerve degeneration ($p = .05$) than placebo-prednisone treatment. The *t*-tests indicated that the recovery profile and index means were significantly better for the acyclovir-treated group (recovery profile $t = 1.99$, $p = .051$; recovery index $t = 2.10$, $p = .040$). We conclude that acyclovir-prednisone is superior to prednisone alone in treating Bell's palsy patients and suggest that herpes simplex is the probable cause of Bell's palsy.

KEY WORDS — acyclovir, Bell's palsy, facial paralysis, herpes simplex, prednisone.

INTRODUCTION

In 1975, we compared viral antibody titers in 40 Bell's palsy patients with those of 40 subjects without Bell's palsy matched for age, sex, race, and socioeconomic level and deduced that reactivated herpes simplex virus was the probable cause of Bell's palsy.[1] Since then, sufficient clinical,[2] laboratory,[3-8] magnetic resonance imaging,[9] and pathology[10,11] data have accumulated to add veracity to the hypothesis that herpes simplex causes Bell's palsy.

On the basis of this knowledge, a clinical trial using the antiviral agent acyclovir (Zovirax, Burroughs Wellcome Co, Research Triangle Park, NC) was justified. Because prednisone had proved beneficial in our previous study,[12] we devised and the Food and Drug Administration approved a double-blind, placebo-controlled research protocol to compare acyclovir-prednisone treatment with placebo-prednisone treatment.

METHODS

Subjects. The patients were subscribers to a prepaid health plan whose membership is broadly representative of the employed population of the San Francisco Bay area and their families with respect to ethnicity, age and sex distribution, and type of occupation.[13] The patients were seen initially in our primary care clinics and emergency departments. After receiving a diagnosis of Bell's palsy, the patients were referred to the Cranial Nerve Research Clinic in Oakland. Study enrollment criteria were 1) that paralysis commenced no more than 3 days before treatment; 2) that patients were over 18 years of age, were in good health as determined by history-taking and physical examination, and had no contraindication for steroid or acyclovir treatment (such as a history of diabetes mellitus, peptic ulcer disease, renal or hepatic dysfunction, connective tissue disease, malignant hypertension, acquired immunodeficiency syndrome, or immunosuppression); and 3) that all women of childbearing age had a negative pregnancy test result.

All study patients agreed to take the medication as prescribed, to return for periodic testing as outlined,

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TABLE 1. CHARACTERISTICS OF 99 PATIENTS ACCORDING TO TREATMENT GROUP

Characteristic	*Acyclovir-Prednisone (n = 53)*	*Placebo-Prednisone (n = 46)*
Age (y)	41.9 (SD 14.1)	44.6 (SD 15.1)
No. of women	24 (45%)	26 (57%)
Right side	24 (45%)	20 (43%)
Recovery profile (mean)	3.0	3.13
Recovery profile of 0 (complete paralysis)	10 (19%)	10 (22%)
Tongue papillitis	53 (100%)	46 (100%)
Cranial nerve V (numbness)	20 (38%)	24 (52%)
Cranial nerve VIII (dysacusis)	12 (23%)	8 (17%)
Cranial nerve X (superior laryngeal paralysis)	7 (13%)	4 (9%)

There was no statistically significant difference between groups.

and not to take any other medication for Bell's palsy, whether prescribed by another physician, purchased over the counter, or already in the patient's possession.

Patients must not have had urea nitrogen or creatinine levels elevated to twice the upper limit of normal, a liver transaminase level >3 times the upper limit of normal, a hemoglobin level of <100 g/L (<10 g/dL), a platelet count of $<75\ 10^9$/L ($<75{,}000$/mm^3), or a total neutrophil count of $<1 \times 10^6$/L ($<1/\mu m^3$).

Of 202 patients referred to the Facial Paralysis Research Clinic, 128 fulfilled the study criteria and 119 enrolled in the trial. Eleven failed to keep scheduled appointments, 7 did not comply with the medication regimen, 1 moved out of the San Francisco Bay area, and 1 stopped taking the medication when a rash developed on the fifth day of treatment. Of the 99 patients who completed the study, 53 received acyclovir-prednisone and 46 received placebo-prednisone. Clinical characteristics and other abnormalities of cranial nerves were nearly identical in both groups (Table 1). Two patients taking acyclovir-prednisone and 3 patients taking placebo-prednisone progressed from incomplete to complete paralysis (recovery profile of 0) during the first week of treatment. Therefore, 19% of the acyclovir-prednisone group (10 of 53) and 22% of the placebo-prednisone group (10 of 46) had complete clinical paralysis representing more severe disease.

Seventy referral patients did not meet the study criteria. Of these, 22 had been seen >3 days after onset of paralysis; 11 had other medical conditions; 9 took other medications; 8 had a history of previous paralysis; and 20 were excluded for a variety of nonmedical reasons, such as failure to sign a consent form or inability to schedule an appointment.

Protocol. All patients read and signed a consent form after receiving full explanation of the details, procedures, and potential risks of the study. The study protocol was approved by the Institutional Review Board of the Northern California Region, Kaiser Permanente Medical Care Program.

The study was double-blind and controlled for treatment, outcome measurement, and electrophysiologic testing. Patients with Bell's palsy were prescribed oral prednisone (1 mg/kg of body weight daily) to be taken in equal divided doses in the morning and evening and were referred to our Facial Paralysis Research Clinic. History-taking and neuro-otologic examination were repeated, and the diagnosis was confirmed. The examination included assessment of paralysis severity measured by the Adour-Swanson facial paralysis recovery profile,[12] referred to here as the recovery profile; audiometry with stapedial reflex testing; and bilateral facial nerve electrical testing. Eligible patients were given identical, unlabeled bottles of 100 capsules that contained either placebo or acyclovir (Zovirax), 200 mg. The bottles, provided by Burroughs Wellcome, were randomized in groups of 10. Each bottle of acyclovir or placebo had a sealed identification label that was removed intact and kept with the patient's record.

Patients were instructed to take 2 capsules 5 times daily, to continue taking the prescribed dosage of prednisone, and to protect their eyes by using dark glasses and artificial tears during the day as well as an oil-based eye ointment before sleeping.

Those taking acyclovir received 2,000 mg (400 mg 5 times daily) for 10 days. All patients received a minimum of 30 mg oral prednisone taken twice daily with meals for 5 days, and the dosage was gradually reduced to 10 mg daily (5 mg in the morning and evening) during the next 5 days. Follow-up appointments were scheduled each week for 2 weeks and each month for 4 months after onset of palsy. All side effects were recorded at each visit. A maximal stimulation test (MST) and electroneurography (EnoG) were performed on the initial visit, 2 weeks, and 2 and 3 months after paralysis onset. The recovery profile was measured at each visit to determine recovery rate. The final outcome, or facial paralysis recovery index,[12] referred to here as the recovery index, was recorded at the last visit. Patients with a recovery profile–recovery index ratio of 10/10 at 3 months after onset of their paralysis were requested but not required to return for further visits. For all other patients, the final ratio of recovery profile to recovery index was recorded at 4 months' time, which in our experience with more than 4,000 Bell's palsy patients is an appropriate end point.

TABLE 2. FPRP AND FPRI

	FPRP: Points Awarded for Each Unit of Recovery*				
Site	*0%*	*1%-25%*	*26%-50%*	*51%-75%*	*76%-100%*
Forehead	0	+1	+1	+2	+2
Eye	0	+1	+2	+3	+4
Mouth	0	+1	+2	+3	+4

Complication	*FPRI† Points*
Contracture	−1
Synkinesis	−1

Adapted and reproduced by permission of publisher from Adour KK, Swanson PJ Jr. Facial paralysis in 403 consecutive patients: emphasis on treatment response in patients with Bell's palsy. *Trans Am Acad Ophthalmol Otolaryngol* 1971;75:1291.

FPRP — facial paralysis recovery profile, FPRI — facial paralysis recovery index.

*Points awarded for facial function on affected side, relative to normal side, in increments of 25%.

†Points subtracted from FPRP to derive FPRI.

Electrical Testing. We conducted serial maximal stimulation testing and EnoG tests in all patients.[14] For all tests, the normal (control) side was studied first and the palsied side second.

The maximal stimulation test was performed with the Hilger model 2-R Facial Nerve Stimulator (WR Medical Electronics Company, Stillwater, Minn).[15] The temporal, orbital, and marginal branches of the facial nerve were stimulated on the unaffected side, and the results were recorded separately. The corresponding nerve branch on the affected side was stimulated at the same setting.

To perform EnoG, the Amplaid mk 15 electrodiagnostic system (Amplaid SPA, Caleppio di Settala, Milan, Italy) was used. The bipolar stimulating electrodes were placed over the stylomastoid foramen, in the groove between the mandibular ramus and the mastoid process, with the stimulating electrode more cranial. The bipolar recording electrodes, encased in a plastic block, were placed in the nasolabial fold, with the recording electrode placed adjacent to the nasal ala. The stimulating electrodes were 6 mm in diameter; the recording electrodes were 7 mm; the centers of the stimulating electrode pair were 23 mm apart; and the centers of the recording electrodes were 25 mm apart. To maximize the muscle compound action potential and to prevent masseter muscle stimulation, only the stimulating electrodes were repositioned. To induce supramaximal stimulation, the intensity was gradually increased until no further CAP increase was noted. The maximum intensity used was 50 mA. The intensity was sometimes limited by masseter muscle contraction or patient intolerance.

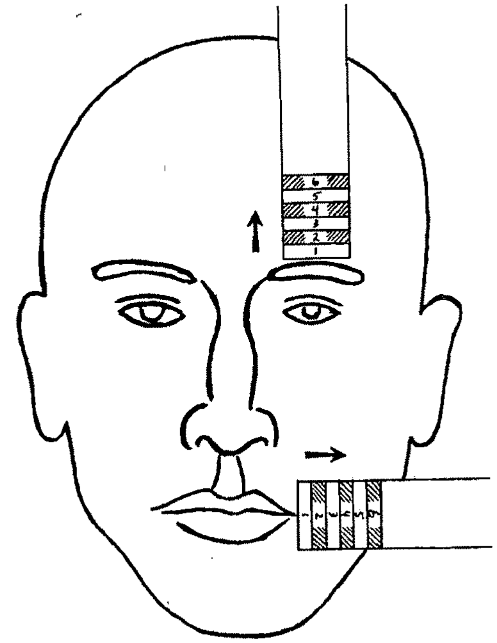

Fig 1. Schematic representation demonstrating measurements used to obtain recovery profile score.

The EnoG findings were inconsistent in predicting nerve degeneration or eventual outcome and could not be used for statistical analysis.[14] The lack of correlation between EnoG results and final outcome has been reported by others.[16]

Global MST. In a previous study, we prospectively and statistically compared the ability of EnoG, facial nerve latency, and MST to predict prognosis in 150 patients who had facial paralysis.[14] The degree of neural degeneration is not always equal in every branch of the facial nerve. Therefore, to more accurately reflect the status of the entire peripheral nerve branch system and to allow more accurate statistical analysis, we devised a numeric method of reporting MST results similar to that used for electromyographic reporting. The amount of muscle movement on the affected side was compared with that on the control side, and the relative response was graded on a scale from 0 to 4. Electromyographic technicians report the estimated degree of muscle action potential (known as interference pattern) on a scale from 0 to 4, with 0 being no muscle action pattern and 4 being a normal response. For MST reporting, 4 is assigned to equal muscle response on both sides of the face, and 3 is assigned to minimally decreased, 2 to moderately decreased, and 1 to severely decreased response compared with that of the same branches on the unaffected side. An MST score was obtained for each peripheral branch, and a mean MST score for all three branches was used for statistical analysis and prediction of prognosis. We refer to the final score as the global MST because it reflects neural activity for the entire face. A mean MST score of ≤2.6 indicated

TABLE 3. CONVERSION FROM FPRP AND FPRI TO HOUSE GRADING SYSTEM

FPRP/FPRI	*House Grade*
10/10	I/VI
10-8/8-6	II/VI
<8/<6	III/VI
*	IV/VI
*	V/VI
†	VI/VI

Criteria used are volitional facial function and presence of synkinesis and contracture. Adapted and reproduced by permission of publisher from Adour KK, Swanson PJ Jr. Facial paralysis in 403 consecutive patients: emphasis on treatment response in patients with Bell's palsy. *Trans Am Acad Ophthalmol Otolaryngol* 1971;75:1291; and by permission of author and publisher from House JW, Brackmann DE. Facial nerve grading system. *Otolaryngol Head Neck Surg* 1985;93:146.

*Synkinesis and contracture are not criteria for these House grades.

†By definition, complete paralysis with no recovery is not Bell's palsy.

clinically significant partial nerve degeneration that would result in incomplete recovery — that is, moderate contracture with synkinesis[14] (House grade III).

Reporting Methodology. Final outcome was graded by using the recovery profile and recovery index. The recovery profile (Table 2) is obtained by measuring the precise amount of forehead and mouth movement (Fig 1) and estimating the degree of eye closure. The affected side is assigned points for each 25% of function relative to the normal side. The forehead is less heavily weighted than the eye and mouth. Percentage of facial muscle function can be estimated by totaling the score from each of the three measurements and multiplying by 10. The recovery index (Table 2) is an adjustment of the recovery profile based on the residua of nerve degeneration and regeneration. Each complication is subtracted from the recovery profile to obtain the final recovery index. For instance, for a patient who had a recovery profile of 10 (76% to 100% volitional facial recovery) but also had a contracture with synkinesis, the recovery index score would be 8 (10 minus 2). As the contracture becomes more severe, there is a lower recovery profile and therefore a lower recovery index. A recovery index of ≤7 (House grade III) is an unsatisfactory clinical result.

The recovery profile and recovery index were used in reporting outcome because this grading system has been used successfully at the Cranial Nerve Research Clinic since 1969, and problems have been identified with the House-Brackmann grading system.[17] However, for uniform reporting of outcome,[18] a method of conversion based on voluntary facial function and degree of contracture and synkinesis to the House grading system is provided (Table 3).

TABLE 4. FPRP, FPRI, AND MAXIMAL STIMULATION TEST RESULTS ACCORDING TO TREATMENT WITH ACYCLOVIR-PREDNISONE AND PLACEBO-PREDNISONE

	Acyclovir-Prednisone (n = 53)		*Placebo-Prednisone (n = 46)*		
Outcome	*No.*	*%*	*No.*	*%*	*p*
All patients					
FPRP of 10	49	92	35	76	.02
FPRI of 10	46	87	33	72	.06
Contracture with synkinesis	7	13	13	28	.06
Maximal stimulation test of ≥2.6	44	86*	32	70	.05
Maximal stimulation test of 0	0	0	0	0	0
Subgroups with complete paralysis†					
FPRP of 10	7	70	5	50	.65§
FPRI of 10	6	60	3	30	.37§

FPRP and FPRI scores ranged from 0 to 10; maximal stimulation test scores ranged from 0 to 4.

*n = 51 (2 patients did not tolerate test).

†n = 10 in each column.

§Fisher's exact test.

Statistical Methods. Univariate comparisons of outcome and electrical tests between the two patient groups were made by using χ^2 analysis and Fisher's exact test. We assessed the statistical significance of the difference in the mean recovery scores by *t*-tests, which at this sample size are fairly robust, to the skewed distribution of the scores. Given that the variance of the scores differed by randomization group, we used Satterthwaite's[19] approximation in the calculation of the significance probability.

RESULTS

Outcome in acyclovir-prednisone–treated patients compared with placebo-prednisone–treated patients is shown in Table 4. In all patient categories, the outcome in patients treated with acyclovir-prednisone was superior to the outcome in patients treated with placebo-prednisone, and statistically more effective in producing return of volitional muscle motion to a recovery profile of 10 (92% versus 76%; p = .02), and more effective in preventing nerve degeneration as measured by electrical tests (87% versus 70%; p = .05) than placebo-prednisone treatment. The *t*-tests indicated that the recovery profile and index means were significantly better for the acyclovir-treated group (recovery profile *t* = 1.99, p = .051; recovery index *t* = 2.10, p = .040; Table 5). Although contracture with synkinesis occurred twice as often and was more severe in those taking placebo-prednisone, the difference in the number of patients with this complication was not significant (p = .06).

TABLE 5. MEAN FPRP AND FPRI BY RANDOMIZATION GROUP

	Acyclovir-Prednisone (mean ± SD)	*Placebo-Prednisone (mean ± SD)*	*p*
FPRP scores			
	9.83 ± 0.64	9.37 ± 1.45	.051
FPRI scores			
	9.57 ± 1.22	8.80 ± 2.19	.040

Complete loss of nerve excitability (global MST score of 0) did not develop in any patient. Of the 20% of patients in each group who had complete clinical paralysis (recovery profile of 0) within 2 weeks of onset, no statistically significant difference in outcome was noted. The lowest recovery index scores were a 5 in the acyclovir-prednisone group and a 2 in the placebo-prednisone group. The final outcome scores (Fig 2) indicate that the placebo-prednisone group had lower final recovery index scores and were 2.7 times more likely to have an unsatisfactory outcome, that is, moderate to severe contracture with synkinesis as indicated by a recovery index of ≤7 (House grade III to IV; 4/53 versus 11/46, p = .024).

Comparison of the rate of recovery for each group was confounded because some patients missed intermediate appointment dates, and accurate statistical analysis was problematic. However, the percentage of patients examined at each interval and the number with a recovery profile of 10 are shown in Fig 3.

Side Effects. Gastrointestinal complaints were the most frequently encountered problems; all such complaints were mild to moderate and did not require treatment.

Scores	Acyclovir-prednisone (n = 53)	Placebo-prednisone (n = 46)
10	46	33
9	0	0
8	3	2
7	1	4
6	1	3
5	2	1
4	0	1
3	0	0
2	0	2
1	0	0
0	0	0

Fig 2. Recovery index scores for all patients (n = 99). Shaded area below line represents unsatisfactory recovery index of ≤7, which indicates moderate to severe contracture with synkinesis (4/53 versus 11/46; p = .024).

DISCUSSION

The hypothesis that herpes simplex causes Bell's palsy had been derived from circumstantial evidence and deductive reasoning. Although animal experimentation has been unable to support the hypothesis that Bell's palsy is caused by compression, work with a mouse model using the Kos strain of HSV-1 has succeeded in producing an acute transient facial paralysis simulating Bell's palsy.[20] Facial paralysis developed between 6 and 9 days after virus inoculation, continued 3 to 7 days, and then resolved. The animals were killed between 6 and 20 days after inoculation. The facial nerves were stained with hematoxylin and eosin and toluidine blue. Viral antigens were detected by means of indirect immunofluorescence and the avidin-biotin peroxidase complex technique. Histopathologically, the affected facial nerve and nucleus manifested severe nerve swelling, inflammatory cell infiltration, and vacuolar degeneration. Herpes simplex virus antigens were also detected in the facial nerve, geniculate ganglia, and facial nerve nuclei. Latent HSV-1 infection in the geniculate ganglia was proven 3 weeks after inoculation.[20]

The clinical finding of inflammation of the fungiform papillae of the tongue in all our study patients (Table 3) confirms the presence of a neuritis in the chorda tympani branch of the facial nerve. Treatment should be based on pathophysiology. When Bell's palsy was thought to be caused by entrapment of the facial nerve in the fallopian canal, surgical facial nerve decompression was appropriate. Studies of T and B lymphocytes,[7,21,22] immune complexes,[7,23,24] cerebrospinal fluid,[3-5,25,26] and serum interferon levels[8] in patients with Bell's palsy suggest that this disease may be a cellular immune response to a viral

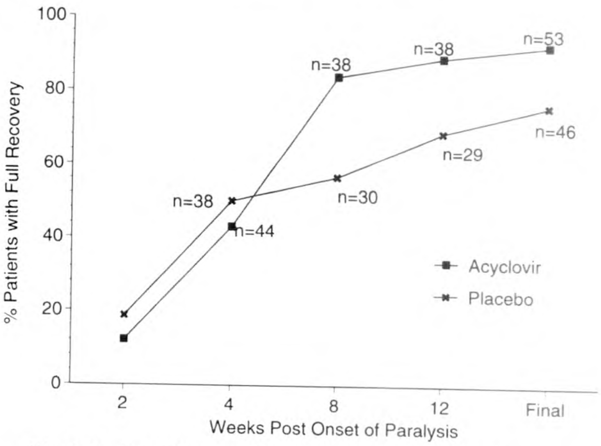

Fig 3. Bell's palsy recovery rate in acyclovir-prednisone group versus placebo-prednisone group as indicated by recovery profile of 10 in percentage of those appearing for examination 2, 4, 8, 12, and 16 (final) weeks after onset of paralysis.

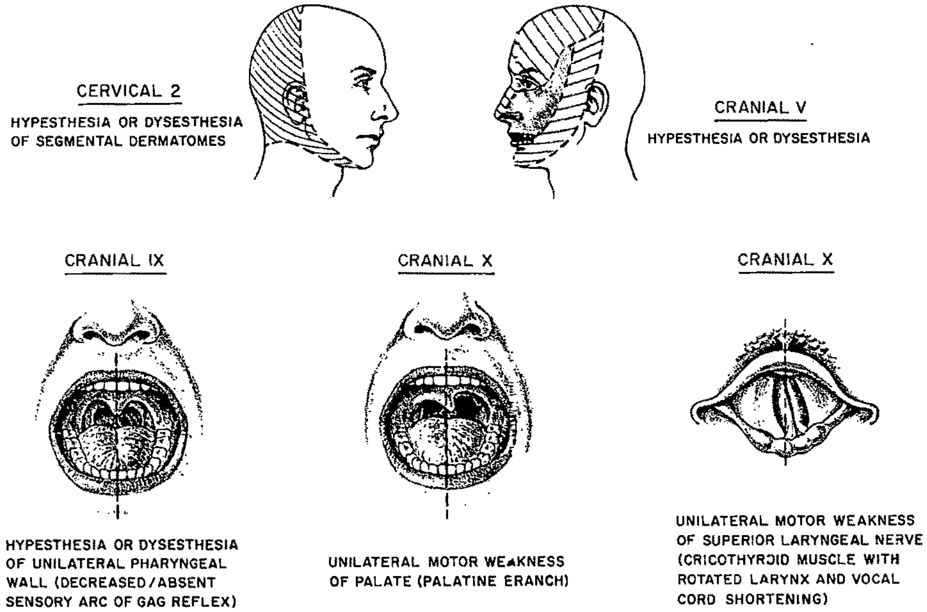
CERVICAL 2
HYPESTHESIA OR DYSESTHESIA OF SEGMENTAL DERMATOMES
CRANIAL V
HYPESTHESIA OR DYSESTHESIA
CRANIAL IX
CRANIAL X
CRANIAL X
HYPESTHESIA OR DYSESTHESIA OF UNILATERAL PHARYNGEAL WALL (DECREASED/ABSENT SENSORY ARC OF GAG REFLEX)
UNILATERAL MOTOR WEAKNESS OF PALATE (PALATINE BRANCH)
UNILATERAL MOTOR WEAKNESS OF SUPERIOR LARYNGEAL NERVE (CRICOTHYROID MUSCLE WITH ROTATED LARYNX AND VOCAL CORD SHORTENING)

Fig 4. Schematic representation of cranial nerve involvement in Bell's palsy and herpes zoster facial paralysis (Ramsay Hunt syndrome). (Reproduced by permission of editor and publisher from House JW, O'Connor AF, eds. *Handbook of neurotological diagnosis.* New York, NY: Marcel Dekker, 1987: 209.)

inflammatory process. If so, steroid treatment would be appropriate: such treatment has already proved effective.[12,27,28] Our decision to use prednisone in both study groups was predicated on this documented beneficial effect.

Although controversy still exists about the efficacy of steroids, complete denervation (global MST of 0) did not develop in any patients in this study. On the basis of our 1972 study, this finding was anticipated, because all patients received prednisone.[12] In that same study, 68% of the prednisone-treated group reached a recovery index of 10; in the present study, 72% of the prednisone-treated group reached a recovery index of 10. No statistical difference in outcome exists between these two studies. Austin et al,[28] in their prospective study, confirmed that prednisone alone is beneficial in preventing denervation, that grade at recovery improved, and that fewer patients had contracture with synkinesis as a direct consequence of nerve degeneration.

Questions persist concerning the appropriate therapeutic dosage of acyclovir, continued use of prednisone, and selection of patients for treatment. The dosage of 2,000 mg daily (400 mg 5 times daily) was selected to maximize intestinal absorption. Theoretically, the dosage of 1,000 mg daily (200 mg 5 times daily) recommended for recurrent herpes simplex virus disease without facial paralysis should suffice. Although side effects were not severe when we used the 2,000-mg daily dosage, decreasing the dosage to 1,000 mg daily may reduce gastrointestinal side effects like those reported in the present study. Ten days of treatment is sufficient, because the active disease process usually ends before that period.

A double-blind treatment study using acyclovir only and acyclovir-prednisone is needed to determine whether prednisone should be prescribed with acyclovir. We believe that prednisone, 30 mg twice daily, or 1 mg/kg of body weight daily for 5 days, gradually withdrawn during the next 5 days, has minimal side effects and should be used with acyclovir.

As the *British Medical Journal* editorialized, "Fortunately most patients with conductive block recover completely. But what should be done within the first three days?"[29(p3)] This raises the unanswered question asked in 1975: "Which patients, if any, are being treated unnecessarily...?"[30(p749)] The often-heard dictum that all patients with Bell's palsy recover almost completely without treatment is erroneous. In the present study, 15% (15 of 99) of patients had an unsatisfactory recovery (recovery index of ≤7) — that is, visible and disconcerting contracture with synkinesis. Moreover, 20% of patients in both groups ultimately had complete paralysis (recovery profile of 0), which indicates severe disease, and no statistical difference in outcome existed between the acyclovir-prednisone and placebo-prednisone groups in those patients who progressed to complete paralysis. Because patients were seen early in the course of their disease, all had been treated with prednisone within 1 or 2 days of onset; we can speculate whether early treatment prevents complete clinical paralysis. In the 1972 study,[12] 42% of untreated patients (46 of 110) had complete paralysis (recovery profile of 0), and only 20% of our present patients, all treated early with prednisone, developed a complete paralysis. Because the 1972 group and the present study group represent different patient populations, no statistical statement can be made about these findings, but they suggest an association between early prednisone treatment and less severe disease.

The disease is progressive for 7 to 10 days,[31] and we are unable to predict which patients will develop the more severe form.[32,33] Therefore, in selecting patients for treatment, relying on deterioration as shown by progression from incomplete to complete paralysis or on results of electrical tests is inappropriate. Nerve conduction does not become abnormal until 3 days after degeneration has occurred. Because treatment is designed to prevent nerve degeneration and later faulty regeneration that leads to midfacial contracture with synkinesis, treatment should begin before electrical test results show abnormalities. Further, Wolf et al[34] showed by diligent electromyographic sampling of the facial muscles that *all* patients have some muscle denervation (as recorded by fibrillation potentials). We advise that all patients start treatment as soon after palsy onset as possible and that treatment be modified 1 week later, depending on whether or not paralysis has progressed.

Cases of Bell's palsy are, fortunately, similar in history, course, and outcome; finding a case of Bell's palsy that deviates from the pattern is unusual, and we are justified in regarding the condition as pathologically the same in all.[2] Bell's palsy can present in a mononeuritic or a polyneuritic form (Fig 4), and it has been suggested that only the mononeuritic form should be included in this study. Limiting the definition of Bell's palsy to the mononeuritic form is not justified. Past definition of "classic" Bell's palsy was based on erroneous data and incomplete physical examination. Bell's palsy symptoms classically include postauricular pain and facial numbness that had been attributed to sensory fibers in the facial nerve. Djupesland et al[35] were the first to report that postauricular pain indicates that cervical nerves II and III are affected. We have reported in numerous articles that the facial numbness represents dysfunction of the trigeminal nerve. We found no statistical difference in outcome when we compared the mononeuritic and polyneuritic forms of Bell's palsy.[32] In accordance with our present knowledge, and to avoid future confusion, we suggest that the term "mononeuritis multiplex" be substituted for Bell's palsy: this term is more comprehensive, because it describes the mononeuritic and the polyneuritic forms.

CONCLUSIONS

When seen within 3 days of onset of paralysis, Bell's palsy patients treated with acyclovir-prednisone had better recovery and less neural degeneration than patients treated with placebo-prednisone. We believe that the favorable response to acyclovir-prednisone treatment of Bell's palsy adds support to the theory that reactivated herpes simplex virus causes this neuritis.

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ADDENDUM

Since the preparation of this report, we have noted another article that supports our findings. Researchers from Ehime University School of Medicine, Ehime, Japan, found HSV-1 DNA in 11 of 14 patients (79%) with Bell's palsy and found varicella zoster virus DNA in 8 of 9 (89%) with Ramsay Hunt syndrome (Murakami S, Mizobuchi M, Nakashiro Y, Doi T, Hato N, Yanagihara N. Bell Palsy and Herpes Simplex Virus: Identification of Viral DNA in Endoneurial Fluid and Muscle. *Ann Intern Med* 1996;124: 27-30). They concluded that the herpes simplex virus is the major etiologic agent in Bell's palsy. The editorial comment (Baringer JR. Herpes Simplex Virus and Bell Palsy. *Ann Intern Med* 1996;124:63-5) suggested we should now recognize Bell's palsy as "herpetic facial paralysis."

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HEARING RESULTS FOLLOWING MODIFIED RADICAL VERSUS CANAL-UP MASTOIDECTOMY

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Modified radical mastoidectomy (MRM) provides relatively safe surgical access for the removal of chronic middle ear and mastoid disease and gives reproducible results. However, it has been suggested that hearing may not be as good as that after "intact canal wall mastoidectomy" (ICWM). This paper reviews 153 tertiary referrals suffering from extensive disease who underwent MRM and compares their hearing results with those obtained by other authors using ICWM and MRM and a variety of reconstructive techniques. In this study there were no dead ears and no significant changes in bone conduction despite prolonged drilling and extensive disease. Hearing results after MRM were found to be better after primary surgery than after revision and better in the presence of an intact stapes. No rigid prostheses were used at first-stage surgery. There were no significant differences found between hearing results obtained by MRM in this series and other published results of canal wall down mastoidectomy and ICWM, irrespective of the use of ossicular replacement prostheses.

KEY WORDS — ear, hearing, mastoidectomy, surgery.

INTRODUCTION

The surgery of chronic suppurative otitis media and cholesteatoma has two main aims: first, the eradication of disease to produce a dry, stable, safe, waterproof ear, and second, the preservation or improvement of hearing. Total removal of disease has traditionally been achieved by radical surgery, which facilitates good visualization and surgical access to all parts of the middle ear and mastoid air cell system. A trend toward so-called hearing preservation procedures in the 1960s and 1970s led to the concepts of "intact canal wall mastoidectomy" (ICWM) and combined-approach tympanoplasty. These procedures were purported to cause less disturbance to normal external and middle ear anatomy and hence to hearing than canal wall down (CWD) modified radical mastoidectomy (MRM), but disease recurrence rates may be high.[1]

As removal of disease must take priority, many authors continue to perform CWD mastoidectomy. The purpose of this paper is to assess hearing results after MRM in a series of tertiary-referral cases of extensive disease and to assess the effect of prolonged drilling on inner ear function.

PATIENTS AND METHODS

One hundred fifty-three patients having undergone MRM were reviewed. All procedures were performed by the senior author (P.A.F.) using the Bien-Air Electric Drill System. The Fisch technique of MRM was employed[2,3] with minor modifications.[4,5] Particular attention was paid to exposure of the sinodural angle and the anterior epitympanum. All bony overhangs were beveled and the mastoid tip was amputated. The tympanic bone was drilled close to its anterior and inferior limits to ensure a wide external canal with a floor below that of the mastoid bowl. The incus or its remnants was removed in every case. The malleus head was removed and the tensor tympani tendon divided to facilitate grafting of the tympanic membrane with temporalis fascia. The handle of the malleus was rarely removed. If the stapes superstructure was found to be intact, a block of conchal cartilage was interposed between it and the neo–tympanic membrane. In a minority of cases in which the stapes superstructure was found to be

TABLE 1. PATIENT DETAILS

Male:female	89:62
Median age (y)	33 (range 6-78)
Median follow-up (mo)	23 (range 3-49)
Primary procedures	83 (68 revisions)
Cholesteatoma present	133
Lateral semicircular canal fistula present	18
Stapes superstructure absent	51

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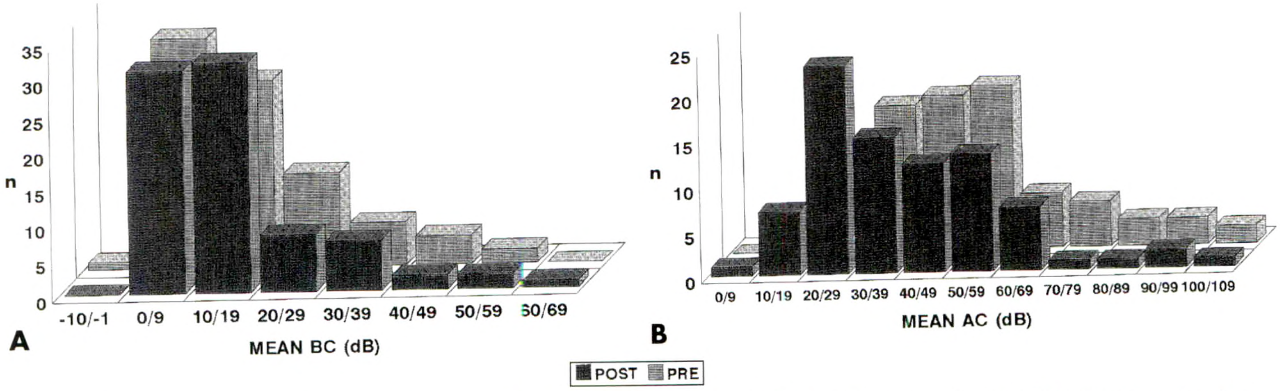

Fig 1. Preoperative and postoperative thresholds averaged over 0.5, 1, 2, and 4 kHz. A) Bone conduction (BC). B) Air conduction (AC).

absent, a figure 7 columella of conchal cartilage was inserted. In no cases was a synthetic total ossicular replacement prosthesis (TORP) or partial ossicular replacement prosthesis (PORP) employed in a primary procedure. Finally, a Fisch-style meatoplasty was fashioned.[1,2] In the absence of cholesteatoma, MRM was indicated by the extent of bone destruction or, occasionally, by disease, but mostly by previous surgery.

Preoperative and postoperative bone conduction (BC) and air conduction (AC) pure tone audiometric thresholds were recorded from 0.25 to 4 kHz. Audiometric data were entered into a spreadsheet (Borland Quattro) and formulae constructed to calculate preoperative and postoperative air-bone gaps (ABGs) and air-bone gap closure (ABGC). Likewise, changes in BC and AC were calculated. A record was also kept of the presence of cholesteatoma, lateral semicircular canal (LSC) fistula, stapes superstructure, and whether the patient was undergoing revision surgery.

Comparisons between preoperative and postoperative audiometric data with reference to the disease parameters were made by means of a spreadsheet-compatible statistical package (Arcus). Statistical analysis was performed by nonparametric methods.

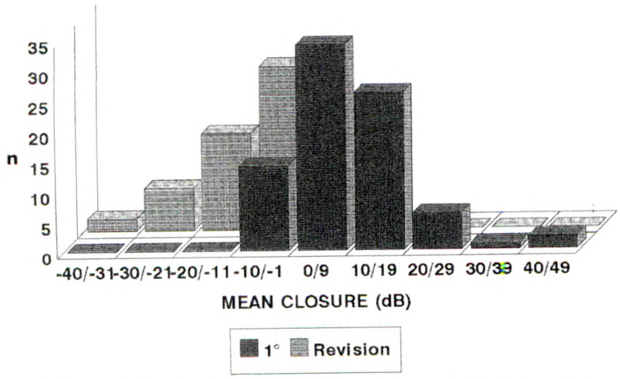

Fig 2. Air-bone gap closure averaged over 0.5, 1, 2, and 4 kHz.

RESULTS

Patient details are given in Table 1. An ear was judged to be dry if healing was complete and the patient could get the ear wet without inducing discharge. The "dry ear" rate in this series was 95%, which is similar to that of a previous series.[5] The median period of follow-up was 23 months. The overall recurrence rate was 3%. Preoperative BC thresholds at 4 kHz correlated with age ($p < .01$, Spearman's rank correlation) and with change in BC (postoperative versus preoperative threshold) at the same frequency ($p < .005$).

Mean preoperative and postoperative BC thresholds for primary surgery, banded into 10-dB intervals, are shown in Fig 1A. The AC thresholds are illustrated in Fig 1B. The averages of thresholds at 0.5, 1, 2, and 4 kHz were calculated. There were no significant changes in BC. The worst individual mean drop in BC was 15 dB, and there were no "dead ears." The median AC improved by 15 dB. Mean ABGCs for primary and revision surgery, again banded into 10-dB intervals, are illustrated in Fig 2. The median ABGC obtained at primary surgery, as opposed to revision surgery, was significantly better when averaged over 0.5 to 4 kHz and at each individual frequency (Table 2 and Fig 2). The fact that there were no significant changes in median BC in

TABLE 2. HEARING RESULTS OF PRIMARY VERSUS REVISION SURGERY

kHz	*Median Difference* in ABG Closure (dB)*	*95% CI (dB)*	*p†*
0.5	15	20, 10	<.0001
1	20	20, 10	<.0001
2	15	20, 10	<.0001
4	15	20, 5	<.0001
Mean§	17	20, 13	<.0001

ABG — air-bone gap, CI — confidence interval.
*Primary minus revision.
†Mann-Whitney U-test.
§0.5, 1, 2, and 4 kHz.

TABLE 3. CHOLESTEATOMA VERSUS NONCHOLESTEATOMATOUS DISEASE

	Cholesteatoma	*No Cholesteatoma*	*p*
Age (y)			<.05
Mean	33.1	43.9	
95% CI	30.5, 35.8	35.3, 42.5	
ABGC (dB)			NS
Mean	1.2	2.7	
95% CI	−1.0, 3.4	−6.1, 11.5	

ABGC — air-bone gap closure (mean of 0.5, 1, 2, and 4 kHz), NS — not significant.

either group indicates that the changes in ABGC were due to changes in AC.

The median improvement in ABG was significantly better in those patients with an intact stapes superstructure (25 dB) than in those without (5 dB) (Mann-Whitney, $p < .001$). This improvement was entirely attributable to an improvement in AC in those with an intact stapes (median change, 25 dB).

No significant difference in mean ABGC was found between patients with cholesteatoma and those without (Table 3). Similarly, patients with LSC fistulae fared as well as those without (Table 4). There was no significant difference in the incidence of LSC fistula in those undergoing primary or revision surgery (Table 5), or between those with and without cholesteatoma (Table 6).

DISCUSSION

Hearing loss after mastoid surgery may be due to changes in the structure of the middle ear or cochlear damage. The latter is usually thought to be due to surgical penetration or suction of inner ear contents, usually through an LSC fistula or in the region of the oval window. While some authors dispute drill noise as a cause of cochlear damage,[6,7] others have found it to be a factor.[8]

Sound pressure levels have been measured during mastoid surgery and found to vary between 84 and 105 dB.[6,8] The use of a high-speed drill system reduces operating time without increasing noise levels.[9] The Bien-Air system employed in the present series provides high torque and a maximum speed of 40,000 rpm, which greatly reduces drilling time.

TABLE 4. PRESENCE OF LSC FISTULA

	Fistula	*No Fistula*	*p*
Age (y)			NS
Mean	40.1	33.6	
95% CI	31.4, 48.8	30.9, 36.3	
ABGC (dB)			NS
Mean	6.0	0.6	
95% CI	−2.7, 14.8	−1.6, 2.8	

LSC — lateral semicircular canal.

TABLE 5. FREQUENCY OF LSC FISTULA IN PRIMARY AND REVISION SURGERY

	Fistula	*No Fistula*
Primary	10	73
Revision	8	60

χ^2 Yates corrected = 0, p = 1.

Hearing results following mastoid surgery are often difficult to compare between series, or even within a series, because of inconsistent terminology and the variety and extent of disease. Black has attempted to address this by determining a "degree of difficulty" for individual ears, the so-called SPITE score (Table 7[10]). He proposes that hearing results are adversely affected by the need for extensive surgery (S), by ossicular discontinuity requiring insertion of a prosthesis (P), by infection (I), by the poor condition of middle ear tissue (T), and by eustachian tube dysfunction as represented by middle ear effusion or posterosuperior cholesteatoma (E). If one allots a score (0 absent, 1 present) to each of these factors, he suggests, a high score will be reflected by a poor hearing outcome and vice versa. All of the cases in the present series scored at least 4, and most were rated as 5. An ABG of less than 30 dB was obtained in 75% of cases with an intact stapes and 58% of cases in which the stapes superstructure was absent following a first-stage procedure. This compares very well with the series of Tos and Lau,[11] who reported results following both MRM and ICWM (Table 8[11-13]).

Assessment of hearing results is usually performed by measuring the ABG, calculated by subtracting the BC threshold from the AC threshold. The gaps at 0.5, 1, 2, and sometimes 4 kHz are then averaged to give a single measure of performance. Unfortunately, there is no consensus on whether preoperative and/or postoperative BC thresholds should be included in the calculation. Perhaps the commonest approach is to compare preoperative and postoperative AC thresholds with preoperative BC thresholds. However, this fails to take into account the effect a drop in BC will have on AC, leading to an underestimation of ABGC. It also ignores the Carhart effect,[14] leading to an overestimation of ABGC. It may be tempting to imagine these factors as canceling each other out, but

TABLE 6. COEXISTENCE OF LSC FISTULA AND CHOLESTEATOMA

	Fistula	*No Fistula*
Cholesteatoma	17	116
No cholesteatoma	1	17

χ^2 Yates corrected = 0.251, p = .617.

TABLE 7. SUMMARY OF "SPITE" ANALYSIS

	Maximum Score for Category
Surgical	1
Proposed complex surgery	
Previous failed ossiculoplasty	
Scutum defect repair required	
Large scutum and eardrum repair required	
Prosthetic	1
Austin* classification of ossicles (malleus and/or stapes absent)	
50-dB air-bone gap present at first presentation	
Infection	1
Unremitting otorrhea	
Chronic myringitis	
Tissue	1
General health	
Myringoplasty required at time of ossiculoplasty	
Meatoplasty significantly impinging on eardrum required	
Mucosa badly damaged at ossiculoplasty site	
Eustachian	1
Preoperative middle ear effusion	
Severe pars tensa collapse present at ossiculoplasty	
Maximum total	5

Table modified from Black.[10]

*Austin DF. Ossicular reconstruction. Otolaryngol Clin North Am 1972;5:145-60.

TABLE 8. HEARING RESULTS OBTAINED IN OTHER SERIES

	Hearing Results (% Patients)		
	<10 dB	*<20 dB*	*<30 dB*
Present study			
CWD MRM, stapes intact	30	69	75
CWD MRM, superstructure absent	12	30	58
Shelton and Sheehy[12] (1990)			
CWD, stapes intact	30	57	77
CWD, superstructure absent	32	54	70
Black[13] (1991)			
"Poor risk," TORP	13	55	NA
"Poor risk," PORP	25	55	NA
Tos and Lau[11] (1989)			
Cholesteatoma, CWD	10	35	62
Cholesteatoma, CWU	24	50	73

CWD — canal wall down, MRM — modified radical mastoidectomy, TORP — total ossicular replacement prosthesis, PORP — partial ossicular replacement prosthesis, CWU — canal wall up, NA — not applicable.

this is clearly not the case. Taking the postoperative BC into account avoids these problems, but makes comparisons with other series difficult. Our results are also presented excluding postoperative BC in Table 8 to facilitate such comparisons.

The results of staged tympanoplasty, with or without mastoidectomy and insertion of a TORP or PORP as reported by Shelton and Sheehy,[12] appear to offer no great advantage over the results of CWD MRM with cartilage interposition between the stapes or footplate and the neo–tympanic membrane as in the present series. Of Shelton and Sheehy's patients undergoing CWD procedures with an intact stapes in their series, the ABG was closed to within 20 dB in 57%. When a reconstruction from the eardrum to the footplate or oval window was required, this figure dropped to 54%. Our figures were 69% and 30%, respectively. Although the insertion of a "Black" TORP[13] does not seem to offer any real advantage over a cartilage strut in the absence of a stapes superstructure, this conclusion may be due to our relatively short follow-up period. A subsequent review of the present cohort of patients is planned to ascertain how many will require a second-stage ossicular chain reconstruction with insertion of a rigid prosthesis.

In this series, no hearing result differences were found between patients with LSC fistula and those without—a finding previously reported by Sheehy.[15]

A correlation was found between a raised preoperative 4-kHz BC and a BC drop after surgery, suggesting that these ears may be at increased risk of further high-frequency loss during mastoid surgery. This finding has previously been reported by Tos et al,[16] but has not been demonstrated statistically before.

CONCLUSION

The present series of 153 tertiary-referral cases with high SPITE scores demonstrates that MRM, properly performed, produces no significant change in BC thresholds and produces overall hearing results that are comparable with those of ICWM procedures.

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MIDDLE EAR MECHANICS IN RESEARCH AND OTOSURGERY

The international workshop Middle Ear Mechanics in Research and Otosurgery will be held in Dresden, Germany, September 19-22, 1996. For further information, contact Prof Dr K. B. Hüttenbrink, Universitäts-HNO-Klinik, Fetscherstr 74, 01307 Dresden, Germany; telephone (Germany) (0)351-458-2224; fax (0)351-458-4326.

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POSTINTUBATION ARYTENOID SUBLUXATION

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Arytenoid subluxation (AS), ie, malpositioning of the arytenoid cartilage with abnormal but existent contact between the joint surfaces, is an uncommon entity, and fewer than 70 cases have been reported, 26 of which were in a recently published series. Usually, AS is the result of upper airway instrumentation, and only a few cases were reported to occur with external trauma to the neck. Some predisposing factors and possible mechanisms have been suggested, but the reason for its occurrence remains obscure. Hoarseness and, to a lesser degree, dysphagia, odynophagia, cough, and sore throat may be indicative of AS. Diagnosis is established by the clinical course, laryngoscopy, and computed tomography. Electromyography and strobovideolaryngoscopy are additional diagnostic measures described. We report 7 cases of postintubation AS of long standing. Three of these patients had prior unilateral vocal cord paralysis, formerly undescribed as a possible contributing factor for AS. The pertinent literature is reviewed and treatment options are discussed.

KEY WORDS — arytenoid cartilage, intubation, larynx, speech, subluxation, trauma.

INTRODUCTION

The terms subluxation and dislocation have been used interchangeably in the literature to describe displacement of the arytenoid cartilage (AC). The term dislocation should be used when there is complete separation of the surfaces of the cricoarytenoid joint, whereas subluxation refers to abnormal but existent contact between the joint surfaces. Arytenoid subluxation (AS), even if underdiagnosed and underreported, is a very uncommon injury. Peppard and Dickens[1] found a 6.3% incidence of traumatic intubation injuries of the larynx in a series of 475 cases, but did not find AS among them. Kambic and Radsel,[2] in a series of 1,000 patients, found a similar percentage of postintubation laryngeal trauma (6.2%), with only 1 case of AS (0.1% of the total or 1.6% of diagnosed injuries). Szigeti et al,[3] reporting on a case of arytenoid dislocation with lighted stylet intubation, also retrospectively reviewed 13,698 intubations performed by their service. Three additional cases of AS were found that were associated with direct laryngoscopy. The calculated incidence from their series is 0.029%. To date, fewer than 70 cases of AS have been described (see Table[2-20]). The majority are in isolated case reports, and only five publications describe more than 1 case.

Sataloff et al[20] recently reported their extensive experience at a referral center with 26 cases of AS. This is the largest number of AS cases reported thus far. Rudert[9] published a report with a large series in the German literature. Although 6 cases are mentioned in his introduction, it may be derived from his table with patient data that there were 9 or even 10 patients with AS. One of his patients had two episodes of subluxation on the same side in two different procedures. Data regarding underlying disease, extent of "prolonged intubation," or exact number of posteriorly versus anteriorly displaced arytenoids are unfortunately lacking. Quick and Merwin[7] describe a homogeneous group of 3 young patients, all with diabetes-induced renal failure and postintubation AS. Tolley et al[16] describe 3 cases of AS associated with difficult intubations, and Hoffman et al[18] describe an additional 3 patients in a comprehensive review of the subject.

Clinical diagnosis of AS supported by proper imaging is not difficult once its presence is suspected. Yet, trauma to the larynx may cause not only AS but also recurrent laryngeal nerve paralysis. Both these entities may present in indirect laryngoscopy with an immobile lateralized vocal cord and an asymmetrically positioned AC.[7,8,12,18] In both instances the history may be similar and indirect laryngoscopy may be equivocal. In the past, confirming the diagnosis of AS required direct laryngoscopy and palpation

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REPORTED CASES OF POSTINTUBATION ARTENOID SUBLUXATION

Case No.	*Authors*	*Year*	*No. of Cases*	*Underlying Disease*	*Intubation*			*Symptoms*				*Side*	*Arytenoid Displacement*
					E	*D*	*P*	*H*	*C*	*D/O*	*S*		
1	Komorn et al[4]	1973	1	–	+			+	+	+		R	Anterior-inferior
2	Prasertwanitch et al[5]	1974	1	+	+			+				L	Lateral-posterior
3	Schultz-Coulton[6]	1974	1	+				+				L	Anterior
4	Quick and Merwin[7]	1978	3	+	1	2	+	+		+	+	L	Lateral-posterior
5	Kambic and Radsel[2]	1978	1	?									
6	Dudley et al[8]	1984	1	+	+			+				R	Medial-anterior
7	Rudert[9]	1984	6 (9?)	?			4	+				4 R, 2 L	"Most were posterior"
8	Chatterji et al[10]	1984	1	–	+							L + R	Anterior
9	Nicholls and Packham[11]	1986	1	–	+			+				L	Anterior
10	Close et al[12]	1987	1	+		+	+					L	Anterior-medial-inferior
11	Roberts et al[13]	1988	1	–								R	Anterior
12	Frink and Pattison[14]	1989	1	–	+			+				L	Posterior
13	Debo et al[15]	1989	1	–		+		+		+		R	Anteromedial
14	Tolley et al[16]	1990	3	–		2	1	+				R	Anteromedial
15	Castella et al[17]	1991	1	–								L + R	Anterior
16	Hoffman et al[18]	1991	3	–				+		+		2 R, 1 L	Anterior
17	Gauss et al[19]	1993	1	–		+		+				L	
18	Szigeti et al[3]	1994	1	+	+			+		+		L	
19	Sataloff et al[20]	1994	26	–		?		22		6		13 R, 13 L	9 Anterior 4 Anteromedial 4 Posterior 5 Not reported 3 Assorted
20	Present study		7	3 With former VC paralysis	4+, 1?	2		+		+		4 R, 3 L	3 Posterolateral 2 Anterolateral 1 Anteromedial 1 Posterior

E — easy, D — difficult, P — prolonged, H — hoarseness, C — cough, D/O — dysphagia and/or odynophagia, S — sore throat.

of the displaced arytenoid. Electromyography (EMG) was shown to assist in diagnosis of AS and in differentiating it from recurrent laryngeal nerve paralysis by recording intact muscular activity reflecting adequate function of the recurrent laryngeal nerve.[12,18,20] Unfortunately, this modality is currently unavailable to us. Computed tomography (CT) has been found to be extremely helpful in the diagnosis of AS.[8,12,18,20] As some imaging features are shared between nerve paralysis and AS, the relationship of the AC to the cricoid cartilage is the definitive diagnostic imaging parameter in the latter. Despite this, only a few of the recent reports on the subject rely on CT, and diagnosis of AS was made in most by clinical evaluation only, with its potential pitfalls. Twelve of 17 patients in the series by Sataloff et al[20] had a diagnosis supported by CT scans. Five patients with no clear radiographic evidence of dislocation had arytenoids that were poorly visualized. Four of the 5 were under 15 years of age, with insufficient mineralization of their laryngeal cartilages.[20] Strobovideolaryngoscopy may define subtle changes in vocal cord motion and was generally found to be beneficial in diagnosis of AS.[20]

Maue and Dickson[21] in a study of 20 adult larynges found the cricoarytenoid facets on the cricoid to be very well defined, consistent, and bilaterally symmetric in all cases. Also, an "extraordinary" degree of similarity was found among all the ACs they examined. The posterior cricoarytenoid ligaments were very noticeable in all larynges (Fig 1). These structures extend from the superior rim of the cricoid lamina, just medial to the cricoarytenoid facet, to the medial surface of the AC.[21] These anatomic findings further support the beneficial application of CT to cricoarytenoid imaging. Magnetic resonance imaging was not shown to be superior to CT in situations in which the interface of the AC and cricoid cartilage is demonstrated.[18]

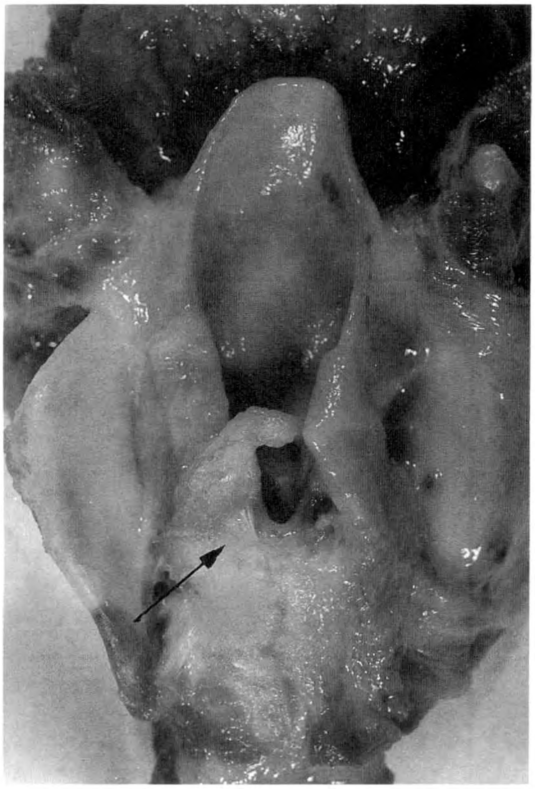

Fig 1. Partially dissected cadaver larynx demonstrates exposed left cricoarytenoid joint. Broad cricoarytenoid ligament is indicated by arrow.

The majority of AS cases are due to instrumentation of the upper airway. Arytenoid dislocation from severe external trauma is usually accompanied by other injuries of the larynx.[22] Eight cases of AS due to external trauma were reported by Sataloff et al,[20] and this incidence seems to be higher than formerly recognized. Three cases of posttraumatic AC dislocation with overlying mucosal tears were reported by Stanley and Colman,[23] and isolated arytenoid dislocation resulting from blunt external trauma to the larynx was described by Stack and Ridley.[24] The displaced joint spontaneously relocated with resolution of edema and hemarthrosis.[24] We report on our experience with 7 cases of AS of long standing.

CASE REPORTS

Case 1. An 89-year-old institutionalized woman with a documented history of unilateral postoperative impairment of vocal cord mobility of over 30 years' duration was admitted for hoarseness and severe stridor of several hours' duration. No data were available regarding the surgical procedure or its course. Physical examination revealed left vocal cord paralysis with mild bowing, a right arytenoid with obvious displacement anterolaterally and inferiorly, and an immobile cord at a near-median position. The patient's respiratory condition rapidly deteriorated and emergency tracheostomy was performed. The right arytenoid was palpated at surgery and was found to be rigidly fixed in its position. Cerebrovascular accident was diagnosed with severe aspiration pneumonia, and the patient died several days later. No imaging was obtained and a request for an autopsy was denied.

Case 2. A 64-year-old man had undergone right hemithyroidectomy 15 years earlier, with documented postoperative recurrent laryngeal nerve paralysis. The patient's hoarseness and weak voice gradually improved at the time, and he did not require any subsequent procedure. One year ago the patient underwent completion thyroidectomy for recurrent goiter. Preoperative indirect laryngoscopy demonstrated an immobile right vocal cord in the paramedian position with good compensatory mobility of the left cord and a good voice quality. Immediately following extubation after the surgical procedure, the patient became hoarse and could hardly phonate. Despite his symptoms, he was referred only months later with only minimal improvement. On examination the patient was hoarse and had a poor cough. The right AC was displaced anteromedially with lateralization of the cord and an incomplete glottic closure. This finding was substantiated by axial CT scan studies. The left cord was fully mobile. Because of the time elapsed, no reduction was advocated, and the patient is considering an offer for a thyroplasty type I procedure.

Case 3. A 66-year-old man underwent coronary artery bypass grafting with a revision because of bleeding 36 hours later. Following the first procedure, the patient presented with a weak voice. Following the second procedure, the patient developed severe respiratory distress necessitating an emergency intubation and tracheostomy. Direct laryngoscopy performed immediately after the tracheostomy demonstrated bilateral vocal cord paralysis and severe edema of the right arytenoid and posterior vocal cord region. Indirect laryngoscopy performed 2 weeks later revealed a paralyzed right vocal cord in the median position and an anteriorly displaced left AC with some lateralization of the posterior part of the left vocal cord. A 2- to 3-mm glottic chink was present on attempted phonation. A CT scan demonstrated a right vocal cord and arytenoid fixed in the median position. The left AC is anteriorly and laterally displaced, with some abduction of the left cord. Because of his poor general condition at the time, no reduction procedure was advocated. The patient is currently using a speech tracheostomy cannula and has declined further surgery.

Case 4. A 44-year-old woman had undergone excision of a left-sided benign parapharyngeal tumor

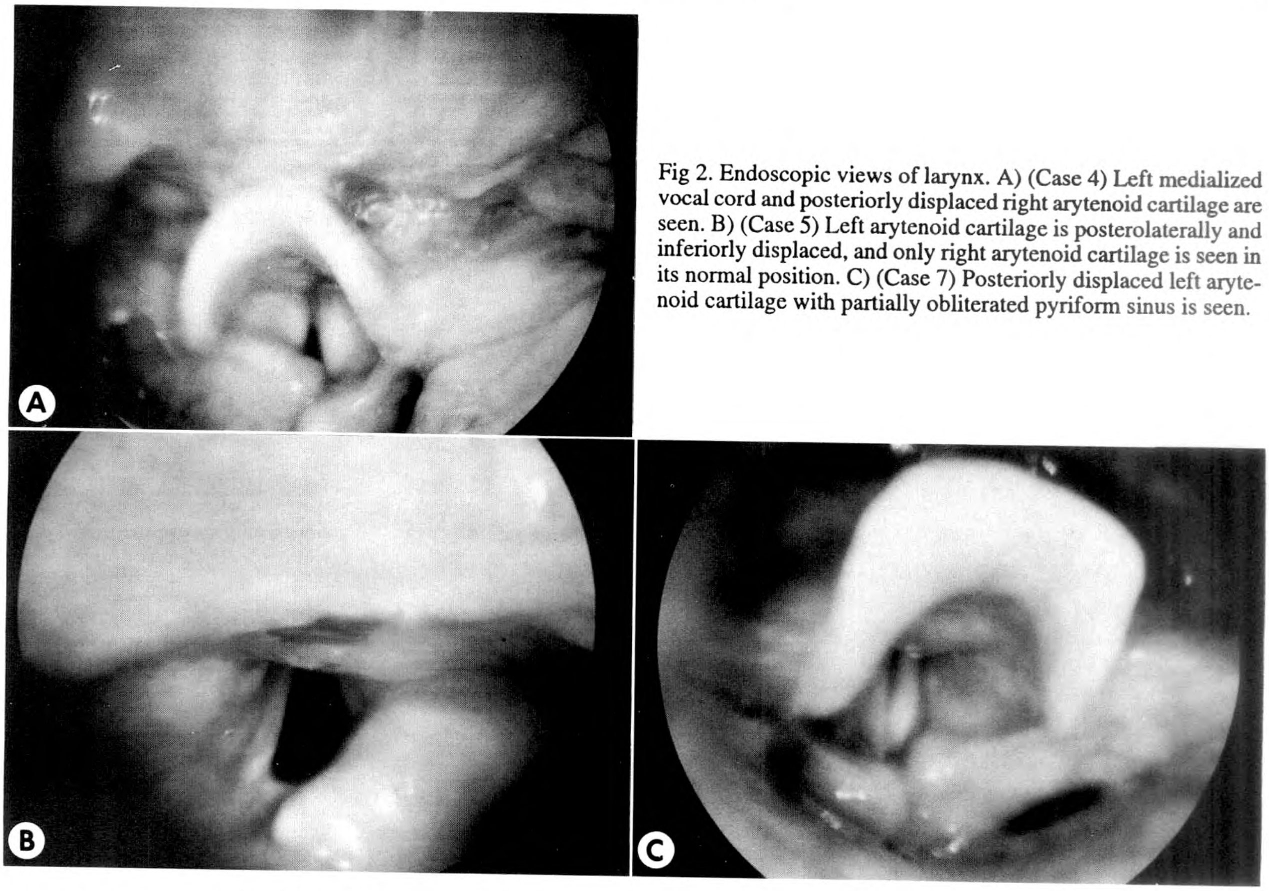

Fig 2. Endoscopic views of larynx. A) (Case 4) Left medialized vocal cord and posteriorly displaced right arytenoid cartilage are seen. B) (Case 5) Left arytenoid cartilage is posterolaterally and inferiorly displaced, and only right arytenoid cartilage is seen in its normal position. C) (Case 7) Posteriorly displaced left arytenoid cartilage with partially obliterated pyriform sinus is seen.

with resulting paralysis of cranial nerves IX through XII. Six months later she underwent Teflon injection to the paralyzed cord with a satisfactory result. Several years later the patient underwent elsewhere a procedure under general anesthesia with resulting postoperative severe respiratory distress. Tracheostomy was considered but the patient, having declined consent, survived. Her situation gradually stabilized and she was discharged and presented in our clinic 6 weeks later. The patient categorically denied any pain or odynophagia at any stage. On examination a paralyzed left vocal cord was seen with posterior displacement of the right arytenoid and a 3-mm glottic opening (Fig 2A). Imaging by CT revealed a Teflon-injected medialized left cord and a posterior and somewhat lateral displacement of the right arytenoid with abduction of the cord (Fig 3). Because of her respiratory compromise, reduction was suggested, with a possible arytenoidectomy should the reduction fail. This patient also declined any further surgical intervention although she is occasionally admitted for respiratory distress.

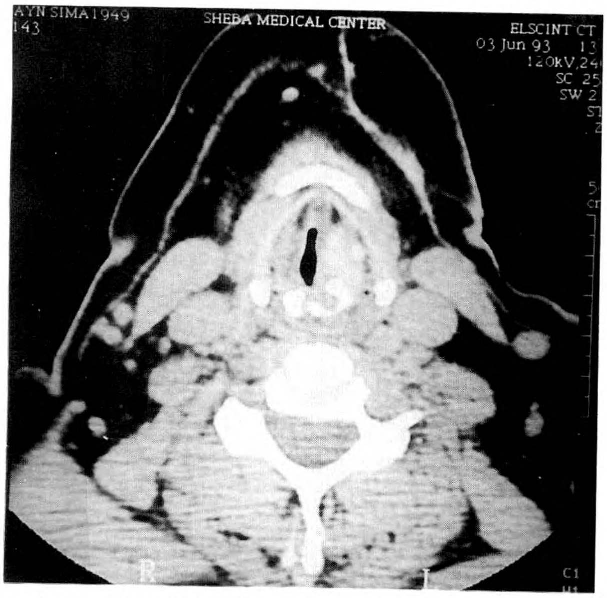

Fig 3. (Case 4) Axial computed tomogram of larynx. Teflon-injected left cord and posterior and somewhat laterally displaced arytenoid cartilage are seen.

Case 5. A 61-year-old man presented with hoarseness of 2 years' duration. The patient had been admitted for observation following a motor vehicle accident and had phonated normally. Three days later he underwent resuscitation with emergency intubation, and he has been hoarse since. On examination, the right cord was freely mobile, with a normally positioned AC, while the left AC was posterolaterally and inferiorly displaced, with abduction of the ipsilateral vocal cord (Fig 2B). Imaging included three-dimensional (3-D) and reconstructed coronal CT scans and showed posterolateral and inferior displacement of the left arytenoid.

Case 6. A 59-year-old man with a history of heavy smoking underwent stripping of his right vocal cord for Reinke's edema 6 years earlier with some improvement of his voice quality, followed 5 months later by stripping of his left cord. Anesthesia records indicate that intubation in the second procedure was difficult and traumatic. Following the procedure the patient was very hoarse and had some dysphagia and odynophagia, all attributed at the time to his procedure. His odynophagia improved and he was discharged, but his hoarseness, albeit somewhat improved, persisted. The patient was lost to follow-up and surfaced only recently, complaining of severe otalgia due to external otitis. Indirect laryngoscopy could not be done, and fiberoptic laryngoscopy revealed anterior-inferior displacement of his right AC with an immobile, laterally positioned right cord. A CT scan demonstrated posterolateral displacement of the right arytenoid, also seen on 3-D CT. Large cervical osteophytes were also seen, probably contributing to the difficulty in viewing and intubating this patient. This patient also declined further treatment.

Case 7. A 67-year-old man suffering from coronary artery disease had undergone cardiopulmonary resuscitation 1 year earlier for cardiac arrest with emergency intubation followed by a 10-day intubation period. Following this, the patient recovered but was found to be suffering from unilateral vocal cord paralysis with contralateral vocal cord paresis. These findings were reported to have improved, but the patient complained of constant hoarseness with fluctuating severity and occasional bouts of mild dyspnea responsive to short-course steroid treatment. The patient was referred to us for evaluation, which revealed a granuloma just under the anterior commissure with a posteriorly displaced left AC (Fig 2C). No imaging studies were obtained. The patient underwent laser evaporation of the granuloma and palpation of the arytenoid, which was found to be frozen in its position, and no reduction attempt was therefore made.

Only 2 of the above patients persisted with speech therapy, with minimal improvement.

DISCUSSION

An anterior, medial, and inferior position of the affected arytenoid viewed on CT would strongly support the diagnosis of AS.[18] This was the finding in only 1 of our cases, while anterolateral displacement was seen in 2 and posterior displacement was seen on another 4 CT scans. Posterior displacement of the arytenoid was thought to present with odynophagia and sore throat,[7] but other reports,[5,14] as well as our experience, do not support this dictum. Hoarseness of various degrees seems to be the hallmark of AS, and complaints of dysphagia, odynophagia, sore throat, and cough are less common. Respiratory distress necessitating airway maintenance may infrequently accompany bilateral subluxation,[10,16,25] although unilateral subluxation in a neonate has also required intubation.[13]

When discussing possible mechanisms for AS, several factors have to be considered. The majority of reported cases are of anterior displacement, but there is also a significant number of posteriorly directed subluxations,[5,7,9,14,20] in which the causative mechanism may be different. Earlier reports also speculated on the seemingly increased prevalence of left-sided AS and attempted to associate this with the direction of introduction of the endotracheal tube.[6,11] A left-right ratio of 26 to 30, excluding 2 cases of bilateral involvement[11,17] and 1 case in which the side was not stated,[2] does not seem to support such a theory. Underlying factors such as diabetes with chronic renal failure, acromegaly, laryngomalacia, ulcerative colitis, and chronic steroid use have also been associated with AS.[5,7-9,13] Resulting weakening of the posterior ligament or degeneration of the cricoarytenoid joint predisposing to subluxation was suggested. Yet, no common underlying disorder has been found, other than in 3 patients with diabetes mellitus reported by Quick and Merwin.[7] Although the majority of patients in earlier reports had an underlying systemic disease,[12] only 11 of the total number of patients with AS described to date had diabetes. Moreover, the possible significance of such disease-related changes is not clear. Casiano et al[26] found no changes in the synovium or joint space itself with increasing age, although progressive regional ossification was observed with periarticular muscular atrophy and fibrosis.

Three of our patients had prior vocal cord paralysis (cases 2, 3, and 4), 2 because of documented severing of the vagus or its recurrent laryngeal branch, and 1 with a suspected similar lesion. In 2 cases, AS was in the contralateral side, and in 1 (case 2), the arytenoid was ipsilaterally displaced. Intubation in such instances is more difficult, and these patients are prone to complications. It is surprising that AS has not been formerly reported to occur in patients with vocal cord paralysis.

Several mechanisms have been suggested for AS. The blade of the laryngoscope has been implicated by several authors.[5,11,12] The force on the tip of the arytenoid is normally directed anteriorly and could thus displace the AC forward and inferiorly. Likewise, the tip of the involved arytenoid could be caught in the lumen of the tube and also be pushed anteriorly and inferiorly.[2,4,12,19] Possible association of the anterior third of the tube and not just the tip was also suggested.[6,7] Similar forces may be applied by a protruding stylet of the endotracheal tube,[4,12,15] bringing about AS.

Posterior subluxation may be more difficult to explain. Posterior displacement has been attributed to a posterolateral force imposed by the convex curvature of the distal (lower) third of the endotracheal tube. The articular surface of the arytenoid could then be found on the sloping shoulder of the cricoid cartilage, posterolateral to its articular surface,[7] as was seen in 3 of our cases. It has also been suggested that withdrawal of the tube with an only partially deflated cuff may deflect the AC and cause trauma.[12,18] In our cases with prior laryngeal paralysis, narrowing of the glottic chink and the fixed midline presence of one cord could have contributed to misdirection of the tip of the endotracheal tube. Szigeti et al[3] found 3 cases of AS that were associated with direct laryngoscopy, but no further data are given. Presumably, as patients undergoing this procedure usually have some laryngeal disorder, its presence may contribute to AS by posing a more difficult intubation. This differential diagnosis is also present in 1 of our patients (No. 6).

We do not believe that AS has a propensity to occur on any side in particular, and find no support for the supposition that the orientation of tube introduction is the cause for mainly left-sided subluxations. Effects of systemic disease are hard to evaluate and quantify, but it is obvious that AS takes place in patients without any underlying disorder of significance. Excluding the series of Sataloff et al,[20] in which intubation data are not given, 6 patients underwent prolonged intubations, and difficult intubations were encountered in only 9 patients, in 1 of whom it was also prolonged. Most ASs were a result of nondifficult intubations. Although it stands to reason that the more difficult the intubation, the more damage can be expected, it is clear that a difficult, traumatic intubation is not a prerequisite for AS.

Delayed spontaneous repositioning of displaced arytenoids has been reported,[9,10,19,20] but awaiting such an occurrence could hardly be advocated. Such a delay may be imposed by the patient's condition, enforcing a period of "wait and see." Treatment with sedatives[25] and spontaneous repositioning following tracheostomy[17] were also described. Treatment of AS should be divided into early and late, although the proposed time frame may significantly vary among authors. Recommended treatment of early AS should be by immediate reduction — and has had reported good results[4,7,8,12,14,20] — perhaps with additional interarticular steroid injections.[9] Sataloff et al[20] report beneficial results of various degrees following closed reduction 6 days to 1 year following AS. Other authors stipulate, however, that the value of reduction is greatly decreased after 1 month. Close et al[12] quote Gosepath's study published in the German literature. In this report, 2 postmortem cases were studied with reference to the cricoarytenoid joint.[12] A study of the joint 24 hours after the injury revealed an early inflammatory response, damage to the synovial layer, and early fibrous ankylosis. In the other case, of an elderly man with long-standing hoarseness, loss of articular cartilage was associated with severe fibrous ankylosis of the cricoarytenoid joint. Experimental dislocations in dogs have shown that joint dysfunction occurs even without violation of the joint capsule, and that even minor degrees of capsular and pericapsular joint fibrosis are sufficient to cause dysfunction.[23] Although good phonatory results were reported with reduction up to 25 days,[9] 5 weeks,[12] or even 1 year after the event,[20] cord movement was impaired. Presumably, reduction attempts of even several-week-old subluxations could cause a "redislocation" of the affected AC and perhaps better position the cord, but it is unlikely that it would become mobile. The report of Sataloff et al[20] certainly gives rise to a new and promising outlook on delayed reduction, but even with their impressive results, we feel reluctant to fully support this procedure, if not done early, without information on cord mobility and voice quality after a longer follow-up period.

Tolley et al[16] performed resection of the malpositioned AC via laryngofissure in 1 case and endoscopic arytenoidectomy in another. This approach may possibly be considered only after exhausting more conservative treatment options.

Late AS should be treated by vocal cord medialization by either Teflon injection or type I thyroplasty. Both these procedures are preferably under light sedation and local anesthesia, allowing some "tailoring" of voice quality. Thyroplasty is the procedure of choice recommended by Hoffman et al[18] in cases of long-standing AS. This procedure was not done in any of the cases of Sataloff et al,[20] although they state that it is probably equal to or even superior to Teflon injection.

Subluxation may be the end result of a multifactorial set of events or just a chance occurrence in a very small percentage of the very large number of intubations performed worldwide. Identifying high-risk patients, including those with an already-paralyzed vocal cord, may limit the occurrence of AS. Large-scale prospective studies of postintubation patients and postmortem histologic examinations of cricoarytenoid joints on both affected and normal sides may be instrumental in clarifying the cause or causes of subluxation. Yet, awareness of its existence and knowledge of proper diagnosis and expedient treatment offer these patients the best chance for preserving normal voice and laryngeal function.

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CARCINOMA OF THE ANTERIOR COMMISSURE OF THE LARYNX: II. PROPOSAL OF A NEW STAGING SYSTEM

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On the basis of embryology and clinical experience, we have defined here an anterior commissure (AC) subsite of the human larynx and have addressed the issue as to whether the degree of involvement of this subsite is related to the outcome of glottic cancer, in terms of local control within 5 years of therapy. Retrospective analysis of 534 patients included 1) classification of patients according to the TNM, 2) actuarial evaluation of the outcome, 3) reclassification of patients according to the involvement of the AC subsite, and 4) reevaluation of the outcome according to this latter classification. The results showed that the outcome was not well correlated with TNM classification, whereas patients with progressively heavier involvement of the AC subsite had a progressively worse outcome. On the basis of these data, we suggest that TNM classification of cancer involving the AC be implemented by an AC classification, in order to better forecast the prognosis and design specific conservative surgery.

KEY WORDS — cancer, larynx, squamous cell carcinoma, TNM classification, tumor staging.

INTRODUCTION

Among the various subsites of the glottic region, the anterior commissure (AC) poses the greatest challenge to investigators and clinicians involved in staging and therapy of larynx cancer.[1-20]

The absence of a universally accepted anatomic and clinical definition of the AC region and the lack of consideration of AC involvement in the principal T stages by the current T classifications of glottic cancer (AJC,[21] UICC[22]) add much to the problem. Since a careful analysis of the human larynx during development allowed us to identify the AC subsite with better detail than previously known, as shown in part I of this paper,[23] we have tried to transfer the results of that study to clinical medicine, as follows.

On the basis of embryology, we have shown that the AC subsite extends on the ventral side of the glottis and in a vertical direction both upward and downward.[24] The AC subsite includes the intermediate lamina of the thyroid cartilage (IL), Broyles' ligament[25] (so-called commissural tendon), which is connected to the IL and behaves as a perichondrium to the latter,[26] the connective tissue between Broyles' ligament and the conoid ligament, and the insertion fibers of the vocal cords.

For clinical purposes, however, the AC region should do the following:

1. Include as much as possible of the AC region as defined on an embryological basis.
2. Exclude definitively the thyroepiglottic ligament and the tissues below the IL.
3. Include definitively the insertion fibers of the vocal cords together with the overlying mucosa with its chorion.
4. Be identified unequivocally from the subglottic region, which has no clear-cut anatomic boundaries at laryngoscopy.

The thyroepiglottic ligament was excluded, because its origin is different from the mesenchymal band that gives rise to the structures of the AC as defined on the basis of embryology.[23] On these bases we have defined the AC clinical subsite as that ventral part of the larynx that is within the IL (before), a frontal plane that passes just behind the anterior fourth of the vocal cords (behind), a horizontal plane passing through the lower extremity of the thyroepiglottic ligament (above), and a horizontal plane passing 10 mm below the glottic plane (below). This last plane coincides with the lower boundary of the glottic region. Laterally, the AC subsite is found between two sagittal planes that pass on both sides along the medial end of the ventricular folds. The anterior fourth of both vocal cords is included between these two planes.

Upon definition of the AC region for clinical use as indicated above, we have addressed in this research the issue of whether involvement of this region by glottic cancer affects the prognosis.

PATIENTS

Between 1970 and 1991, 534 patients with primary

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TABLE 1. METHOD OF PATIENT TREATMENT ACCORDING TO TNM

T Stage	Primary Treatment Surgery	Radiotherapy	Total
T1a	9 EC 277 C 55 FL	8	349
T1b	1 C* 36 FL 2 TL 4 OS	52	95
T2	12 C 21 FL 3 CHP 14 TL 2 OS	21	73
T3	13 TL	1	14
T4	3 TL		3
Total	452	82	534

EC — endoscopic cordectomy (none performed by laser), C — cordectomy, FL — frontolateral laryngectomy, TL — total laryngectomy, OS — other conservation surgery (horizontal glottectomy, frontal-anterior laryngectomy), CHP — cricohyoidopexy.

*Bilateral cordectomy for simultaneous cancer.

glottic cancer arising within the anterior two thirds of the vocal cords were treated with curative intent at the Institute of Otorhinolaryngology of the University of Florence; these patients included cases with (309 cases) or without (225 cases) involvement of the AC. In 78 of the 309 patients with AC involvement, cancer was restricted only to the AC subsite, as seen on direct and indirect laryngoscopy. During this period, patients either underwent surgical procedures (452 cases) or received primary radiotherapy (82 cases). The mean age of patients was 51.4 years (range 28 to 86 years).

Patients were classified according to the TNM system of the International Union Against Cancer (1987)[22] for glottic cancer as follows: 349 T1a, 95 T1b, 73 T2, 14 T3, and 3 T4.

Neck dissection was performed simultaneously with the surgical therapy of the glottic cancer only in 4 cases (1 T2 and 3 T3), 2 of which had positive neck lymph nodes (N1) at diagnosis. A delayed homolateral neck involvement was observed in 20 cases. On the whole, therefore, 24 of 534 (4.5%) patients were affected by laterocervical lymph node metastases. The method of primary treatment was selected only on the basis of the T classification and is detailed in Table 1.

Patients with T1b or T2 tumors were treated with operations other than frontolateral laryngectomy (FL) either because — preoperatively or at the intervention — the tumors appeared to extend beyond that part of the larynx that can be excised with FL, or because of poor general conditions.

Eighty-two patients were treated by radiotherapy (Co^{60}). Two anterior oblique, 6 × 7-cm wedged fields

TABLE 2. LOCAL CONTROL IN 534 PATIENTS WITH GLOTTIC CANCER CLASSIFIED ACCORDING TO TNM (309 CASES WITH AC INVOLVEMENT AND 225 CASES OF MIDDLE THIRD OF VOCAL CORDS WITHOUT AC INVOLVEMENT)

Patients	TNM	Excluded*	First Therapy Surgery		RT	Local Control at 36 mo	Salvaged or Attempted TL	Other Surgery	RT	Ultimate Local Control at 60 mo
349	T1a	54	289	6 EC 236 C 47 FL	6	278/295† (94.2%)	10/10	5/5	1/1	294/294† (100%)
95	T1b	23	36	30 FL 4 OS 2 TL	36	51/72 (70.8%)	13/16	4/4	1/1	69/72 (95.8%)
73	T2	20	42	12 C 17 FL 3 CHP 8 TL 2 OS	11	44/53 (83%)	5/5	4/4		53/53 (100%)
14	T3	7	7	7 TL		7/7 (100%)				7/7 (100%)
3	T4	3								
534 (total)		107	374		53	380/427 (89%)	28/31	13/13	2/2	423/426† (99.3%)

AC — anterior commissure, RT — radiotherapy, TL — total laryngectomy, EC — endoscopic cordectomy, C — cordectomy, FL — frontolateral laryngectomy, OS — other conservation surgery (horizontal glottectomy, frontal-anterior laryngectomy), CHP — cricohyoidopexy.

*Patients with follow-up of less than 36 months.

†One patient with recurrence at 36 months was lost to follow-up.

TABLE 3. LOCAL CONTROL IN 534 PATIENTS WITH GLOTTIC CANCER CLASSIFIED ACCORDING TO AC IN ADDITION TO TNM

					First Therapy			*Salvaged or Attempted*			
Patients	*TNM*	*Excluded**	*TNM*	*AC*	*Surgery*	*RT*	*Local Control at 36 mo*	*TL*	*Other Surgery*	*RT*	*Ultimate Local Control at 60 mo*
225	222 T1a 1 T1b 2 T2	36	187 T1a 2 T2	AC0 189	188 3 EC 184 C 1 FL	1	180/189† (95.2%)	6/6	1/1	1/1	188/188† (100%)
155	127 T1a 1 T1b 24 T2 3 T3	22	108 T1a 1 T1b 22 T2 2 T3	AC1 133	126 3 EC 64 C 56 FL 3 TL	7	121/133 (91%)	6/6	6/6		133/133 (100%)
140	93 T1b 41 T2 6 T3	39	71 T1b 26 T2 4 T3	AC2 101	56 36 FL 3 CHP 11 TL 6 OS	45	76/101 (75.2%)	15/18	6/6	1/1	98/101 (97%)
14	6 T2 5 T3 3 T4	10	3 T2 1 T3	AC3 4	4 1 FL 3 TL		3/4 (75%)	1/1			4/4 (100%)
534 (total)		107		427	374	53	380/427 (89%)	28/31	13/13	2/2	423/426† (99.3%)

AC — anterior commissure, RT — radiotherapy, TL — total laryngectomy, EC — endoscopic cordectomy, C — cordectomy, FL — frontolateral laryngectomy, CHP — cricohyoidopexy, OS — other conservation surgery (horizontal glottectomy, frontal-anterior laryngectomy).

*Patients with follow-up of less than 36 months.

†One patient with recurrence at 36 months was lost to follow-up.

were used. A total dose in the range of 5,600 to 6,700 cGy was delivered in fractions of 200 cGy, 5 days a week. Radiotherapy was employed 1) in patients with small AC lesions involving both vocal cords, 2) in older patients, 3) in patients with unsatisfactory general conditions, and 4) in patients who refused surgery.

METHODS

To answer the issue raised in the Introduction we first revised the outcome of the patients as a function of TNM staging (Table 2), then divided the patients into subgroups according to the degree of involvement of the AC and analyzed the outcome as a function of that involvement (Table 3). In all cases therapy had been selected on the basis of TNM classification of tumors, without taking into account the degree of involvement of the AC region. The patients were classified into four subgroups.

1. Patients without any involvement of the AC region (AC0).
2. Patients with involvement of the AC region on only one side of the midline (AC1).
3. Patients with involvement of the AC region that crosses the midline on only part of the longitudinal extension of this region (AC2).
4. Patients with involvement of the whole AC region, on both sides of the midline (AC3).

Each of these subgroups included patients with different extents of tumor according to the TNM classification, as detailed in Table 3.

As a result, local control within 5 years of surgery was considered. Some cases with local recurrences were further treated to attempt salvage, and the ultimate local control rate was also evaluated.

Data on the outcome within 5 years of therapy are presented in Tables 2 and 3. For these Tables all patients with a follow-up of less than 3 years were excluded. The number of excluded patients is indicated in Tables 2 and 3.

The Kaplan-Meier actuarial method was used for statistical analysis, so that it was possible to take into account all patients entering the study, independent of the time of follow-up.[27] Differences in survival rates were analyzed by χ^2 test.[28] Levels of $p < .05$ were assumed as significant.

RESULTS

Primary Local Control. The rate of local recurrence was significantly different among the subgroups of patients, both when the subgroups had been formed on the basis of TNM classification and when they had been formed on the basis of AC classification (Tables 2 and 3; Fig 1).

Most important, the rate of recurrence increased progressively with the AC class, whereas no such correlation was found between that rate and TNM class. In particular, patients with T3 cancers had a

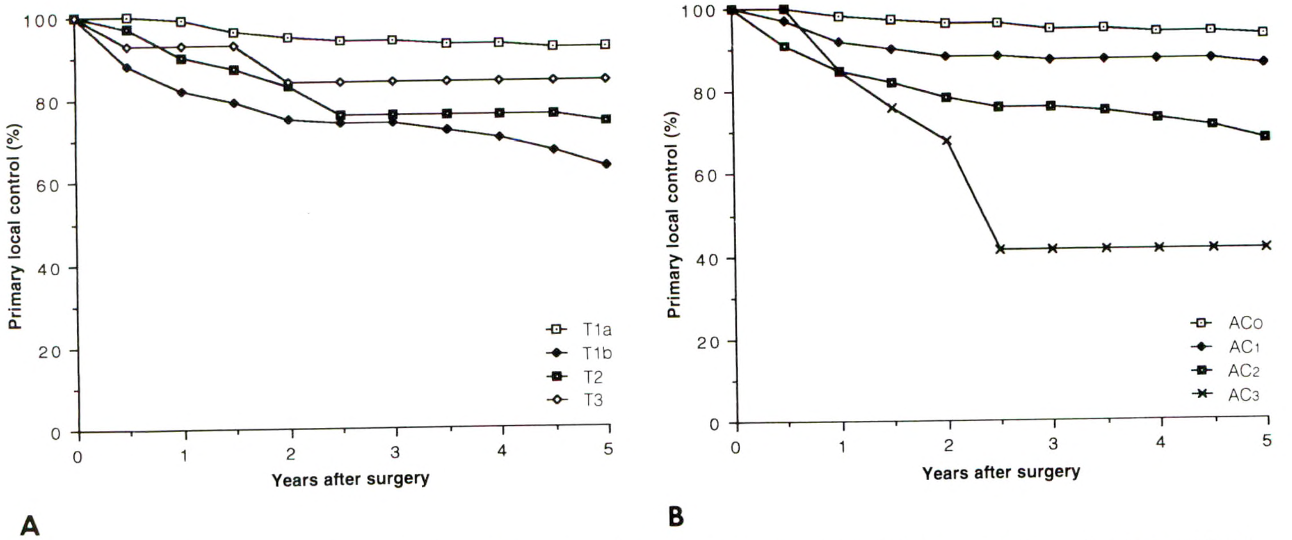

Fig 1. Actuarial analyses of primary local control rate of patients. Curves represent cumulative percentages of patients without local recurrence at each time point from surgery or radiotherapy. A) As function of TNM classification. B) As function of anterior commissure (AC) classification. Differences among subgroups of patients are significant (p < .001).

lower rate of local recurrence than those with T2 cancers, and these latter patients, in turn, had a lower rate of local recurrence than those with T1b cancers (Tables 2 and 3; Fig 1).

Ultimate Local Control. In some cases in which local recurrence occurred, it was treated successfully by surgery or radiotherapy (Tables 2 and 3; Fig 2). This led to an improvement in the ultimate local control rate of all the patient subgroups formed on the basis of AC classification and of the patient subgroups formed on the basis of TNM classification, except for patients with T3 and T4 cancer.

However, even for ultimate local control, the correlation between staging and rate of recurrence remained stringent for AC classification but not for TNM classification.

Relationship Between TNM and AC Staging. It should be noted that each subgroup formed on the basis of AC classification included patients in different TNM stages (Table 3). No patient with T1 cancer was included in the AC3 subgroup, and no patient with T3 or T4 cancer was included in the AC0 subgroup. Patients with T4 cancers, in particular, were restricted to the AC3 subgroup. Patients with T1a cancers were restricted to the AC0 and AC1 subgroups; the exclusion of these patients from the AC2 subgroup depended on the definition of this latter subgroup (cancer going over the midline on part of the longitudinal extension of the AC region). One

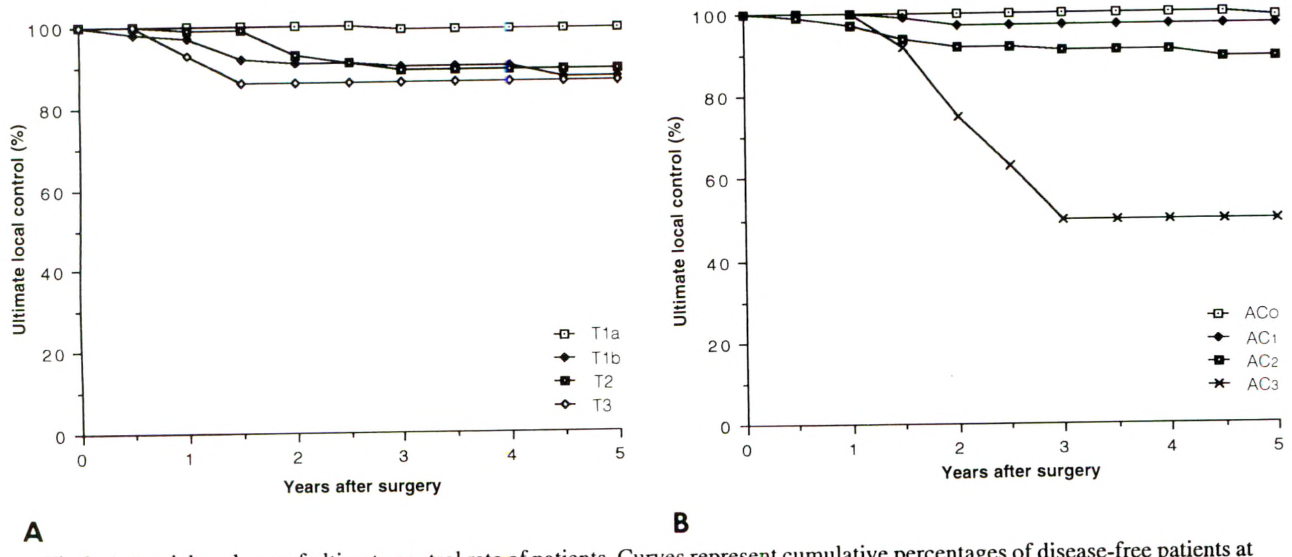

Fig 2. Actuarial analyses of ultimate control rate of patients. Curves represent cumulative percentages of disease-free patients at each time point from surgery or radiotherapy (including salvaged). A) As function of TNM classification. B) As function of anterior commissure (AC) classification. Differences among subgroups of patients are significant (p < .001).

patient with T1b cancer was included in the AC0 subgroup and one in the AC1 subgroup, because they were affected by independent and simultaneous cancers of the two vocal cords.

DISCUSSION

The results of this study show that involvement of the AC subsite by glottic cancer is reflected in the prognosis, whereas prognosis is not well correlated with TNM classification. As far as local control is concerned, there is a correlation with AC classification. The prognosis, as evaluated from actuarial curves of local recurrence-free time, progressively worsens from AC0 to AC3 classes.

The results of this clinical investigation tell us the importance of the data reported in part I of this paper.[23] In fact, it is necessary to consider the limits of the AC to explain the results of the present paper (part II), and the AC subsite of the larynx could only be recognized and properly defined on the basis of embryology.

The apparent paradox of progressively worse local control in the order T3, T2, T1b can be explained by the fact that tumors in more advanced TNM classes are treated with more extensive surgery, whereas those in less advanced TNM classes are treated with conservation surgery. The data can be interpreted as indicating that the success of conservation surgery, in terms of local control, is heavily influenced by the degree of involvement of the AC, which, if properly considered, would lead to more efficient therapy, tailored to the individual.

The limited efficiency of TNM classification in predicting prognosis can thus be explained by the fact that this classification does not take into account the subsites into which an organ such as the larynx can be divided.[17-20] On the contrary, specific surgery is aimed at sparing as much as possible of the structure, and hence of the function of the organ. Therefore, additional criteria should be considered, beyond those of TNM classification, to plan therapy and forecast prognosis in patients with laryngeal cancer. We propose that AC classification be introduced in addition to TNM for cancer involving the AC; AC classification should not substitute for TNM classification, but rather should integrate it with additional criteria for specific conservation surgery.

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HEALING OF TYMPANIC MEMBRANE AFTER MYRINGOTOMY DURING *STREPTOCOCCUS PNEUMONIAE* OTITIS MEDIA

AN OTOMICROSCOPIC AND HISTOLOGIC STUDY IN THE RAT

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The purpose of our study was to elucidate the course of healing of the tympanic membrane (TM) when myringotomy was performed during acute otitis media. The early and long-lasting structural changes of the TM were studied in an animal model. Rats were inoculated with *Streptococcus pneumoniae* (PnC) type 3 in the bulla. When the infection was manifest, myringotomy was performed. On days 4 and 12, and 3 and 6 months after myringotomy, the TM status was checked by otomicroscopy and TMs were prepared for light and electron microscopy. Comparison was made with PnC-infected TMs that were not perforated, as well as myringotomized noninfected TMs. The infection resolved more slowly in myringotomized ears compared to PnC-infected ears that were left untouched. After 6 months, the pars tensa of the myringotomized infected ears was thickened and showed a disorganized collagen structure, compared with myringotomized noninfected ears, in which TMs were normalized. The PnC-infected TMs without myringotomy were completely normalized after 2 months. We conclude that a combination of bacterial infection and myringotomy causes long-lasting changes in TM structure. This impaired structure of the connective tissue could be of importance in chronic middle ear disease as a presumptive site for retraction and perforation of the TM.

KEY WORDS — myringotomy, rat, *Streptococcus pneumoniae*, tympanic membrane.

INTRODUCTION

Acute otitis media (AOM) is a common infection among young children, especially in the age group 6 to 11 months.[1] As many as 50% of all children have had at least one episode before age 3, and 75% before age 10.[2] Many children suffer from recurrent episodes of AOM.[1-3] The bacterial agent most often involved in AOM is *Streptococcus pneumoniae* (PnC), found in 35% to 60% of all cases, followed by nontypeable *Hemophilus influenzae* as the second most common pathogen.[4-6] For uncomplicated episodes of AOM, treatment for 5 days with penicillin V, 25 mg/kg of body weight twice daily, in combination with analgesics is an effective and generally accepted standard treatment in Sweden.[7] Others recommend drainage of the middle ear by myringotomy, with or without parallel antibiotic treatment, as treatment of AOM.[8-10]

In one study, when tympanic membranes (TMs) perforated spontaneously during PnC infection, there was scar formation and newly formed bone in the connective tissue layer of the pars tensa after 2 months.[11] By contrast, TMs that healed without perforating showed no structural changes. This suggests that a perforation in an infected TM causes long-lasting changes in the TM structure.

Several experimental studies have dealt with the healing capacity of the TM after myringotomy.[12-14] However, these studies were made on healthy animals whose TMs were not affected by bacterial infection at the time of myringotomy. The aim of the present study was to analyze the clinical course of myringotomized ears during PnC AOM, and to see to what extent the myringotomy will lead to scar formation in the TM.

MATERIALS AND METHODS

Nineteen male Sprague-Dawley rats, weighing 250 g, were used in the experiment. All animals were free of middle ear infection when included in the study, as judged by otomicroscopy. They were kept under standard laboratory conditions and were given pellets and water ad libitum. When the animals were inspected under the otomicroscope or operated on, they were anesthetized and a short-acting barbiturate, methohexital (Brietal), was given intravenously via a tail vein. The right tympanic bulla was reached through a ventral incision in the neck. The bulla was punctured with a fine needle and filled completely (approximately 0.05 mL) with Todd-Hewitt broth

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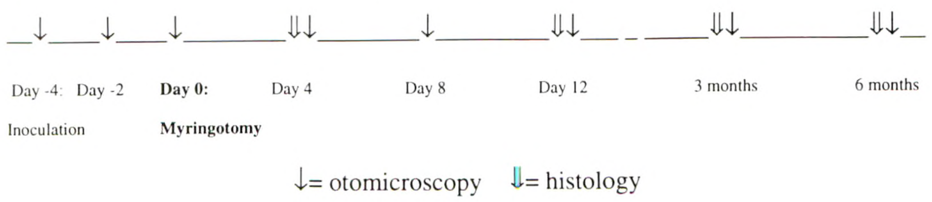

Fig 1. Schematic outline of experimental design.

containing viable log phase PnC type 3, in a dose of 10^7 colony-forming units (CFU) per milliliter. Bacteria were cultured by Dr Hermansson at the Department of Microbiology, University of Lund. The TMs of the right ear constituted the group *infected ears with myringotomy*. The left bulla was untouched, and TMs of these ears constituted the group *noninfected ears with myringotomy*.

At 4 days after inoculation, the animals showed a TM status of manifest AOM, and myringotomy was performed in all ears, ie, both the right, inoculated ear and the left, control ear. The myringotomy was performed with a fine, sharp injection needle, causing a perforation occupying the upper rear quadrant of the pars tensa. Otomicroscopy was performed at inoculation, 2 days after inoculation, at myringotomy (day 0), at 4, 8, and 12 days, and at 3 and 6 months after myringotomy on all rats remaining in the experiment (Fig 1).

Four and 12 days and 3 and 6 months after paracentesis, 4 randomly selected animals were killed on each occasion. The ears were checked otomicroscopically under anesthesia with Brietal, and the rats were thereafter given anesthesia with pentobarbital sodium intraperitoneally. Intracardiac perfusion was performed with 3% glutaraldehyde solution in 0.1 mol/L sodium cacodylate buffer with 4% polyvinylpyrrolidone and 2 mmol/L calcium chloride added. The perfusion lasted for 10 minutes, then the heads were removed and immersed in the same fixative for at least 1 week. Later, the TMs were excised under an otomicroscope and the pars tensa and the pars flaccida were separated. After a brief rinse in buffer, the specimens were postfixed for 2 hours in 1% osmium tetroxide added in buffer. After another rinse, they were dehydrated in increasing concentrations of acetone and embedded in an Epon mixture, Polybed. The TMs were cut into 1-μm sections through the perforated area and stained with toluidine blue for light microscopy. Myringotomized PnC-infected and noninfected TMs of the 3-month and 6-month groups were prepared for transmission electron microscopy. Ultrathin (70 nm) sections were cut in an ultramicrotome and stained with uranyl acetate and lead citrate.

Tympanic membranes from 3 healthy, untreated rats were used as normal references and were prepared in the same way as described above. The normal appearance of TMs of the Sprague-Dawley rat has already been thoroughly described,[15-18] and is not included in the present results.

In addition, the preparations from the present experiment were compared with those from earlier studies on PnC-infected TMs that were not myringotomized.[11,19] These experiments had been carried out under the same laboratory conditions as the present experiment. These TMs are in this paper referred to as *infected ears without myringotomy*. Note that this group is analyzed at defined intervals after inoculation of bacteria, in contrast to the other groups, which are referred to by the day of myringotomy.

RESULTS

INFECTED EARS WITH MYRINGOTOMY

Otomicroscopic Findings. Two days after inoculation, all animals developed a purulent effusion medial to the TM. Four days after inoculation (day 0), when myringotomy was performed, the middle ears had filled with purulent effusion in all cases (Fig 1).

Four days after myringotomy the wound was reduced in size. In some cases, the perforation was covered with a blood clot. A purulent effusion was still present in the middle ears, either medial to the whole TM, or in the superior parts only.

Eight days after myringotomy a purulent effusion was seen in the attic in most cases. All perforations had healed, and in only a few cases, sclerotic inlays (sclerosis) in a horseshoe-shaped pattern were found. Blood vessels were prominent in the pars flaccida and along the handle of the malleus.

At 12 days after myringotomy, vessels were dilated in the pars flaccida and along the handle of the malleus. Sclerosis was found in the same TMs as in the observation at day 8. A purulent effusion was still present in the majority of cases. In cases in which no purulent effusion remained in the middle ears, the pars flaccida was whitish, indicating increased thickness.

After 3 and 6 months the TMs were thickened at the perforated area and there was sclerosis formation.

Histopathologic Findings. On day 4 (Fig 2) the pars tensa was thickened and there was a pronounced

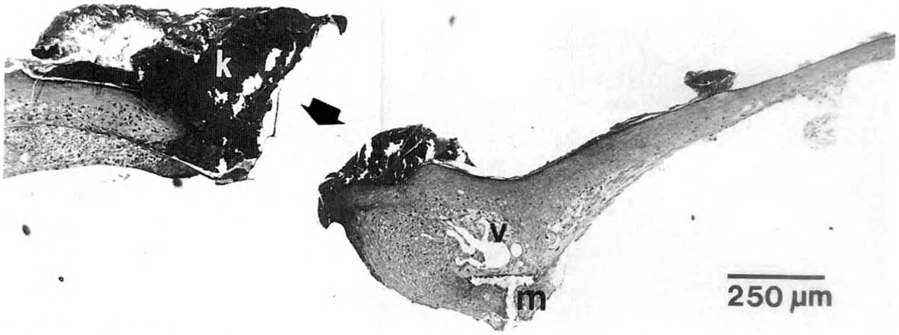

Fig 2. Light micrograph of pars tensa of *Streptococcus pneumoniae* (PnC)–infected ear 4 days after myringotomy (toluidine blue, original ×60). Shows handle of malleus (m) centrally, perforation of pars tensa (arrow), and dilated vessels (v). Keratin (k) has accumulated at perforation edges.

inflammatory response. Polymorphonuclear neutrophils (PMNs) infiltrated the stoma. At the perforation site, the pars tensa was extremely thick and there was a thickening of both the keratinizing epithelium and the connective tissue layer. Keratinocytes were growing around the margin of the perforation. Capillaries were extremely dilated at the handle of the malleus. The lamina propria of the pars tensa was thick even at sites that had not been perforated. Along the inner epithelium were scattered PMNs, and a few PMNs were seen in the stroma. In the nonperforated areas of the TM, the outer and inner epithelia were of normal thickness. The pars flaccida was edematous and mast cells were degranulated. The keratinizing epithelium was slightly thickened. The blood vessels were extremely dilated. Scattered PMNs were seen in the stroma. The inner epithelium was cuboidal. Large vacuolated cells resembling macrophages were located along the inner epithelium.

On the 12th day (Fig 3) after the perforation, the connective tissue and the keratinizing epithelium were still extremely thick. The TM structure was reestablished, with an outer keratinizing epithelium, a middle layer with connective tissue, and an inner simple squamous epithelium. Islands of keratinizing epithelium were seen in the connective tissue. Blood vessels were dilated. Sporadic PMNs were present. At sites in which the pars tensa had not been perforated, the structure appeared completely normalized. The pars flaccida was edematous, with dilated vessels. The outer epithelium was thickened and the inner epithelium appeared normal.

At 3 months after myringotomy, 3 of the specimens showed normalized pars tensa, while 1 specimen showed a thickened stroma at the perforation site.

Six months (Figs 4 and 5) after myringotomy the pars tensa was thicker than normal except in 1 case (12.5, 20, 65, and 5 µm, respectively). In some sections, bone tissue occupied the stroma. No inflammatory cells were observed. Electron microscopy showed an altered collagen structure. There was no uniform orientation of the collagen bundles; they were spread through the stroma in a disorganized manner. The outer epithelium was thickened. The pars flaccida was normal.

NONINFECTED EARS WITH MYRINGOTOMY

Otomicroscopic Findings. No inflammatory reaction was seen in the left ear in any of the animals 2 or 4 days after inoculating PnC into the right bulla. When inspected on day 4 after myringotomy, the perforations had not diminished. No signs of fluid or infection were apparent in any of the ears. Vessels were prominent along the handle of the malleus, and in 1 of 5 cases, sclerosis was observed.

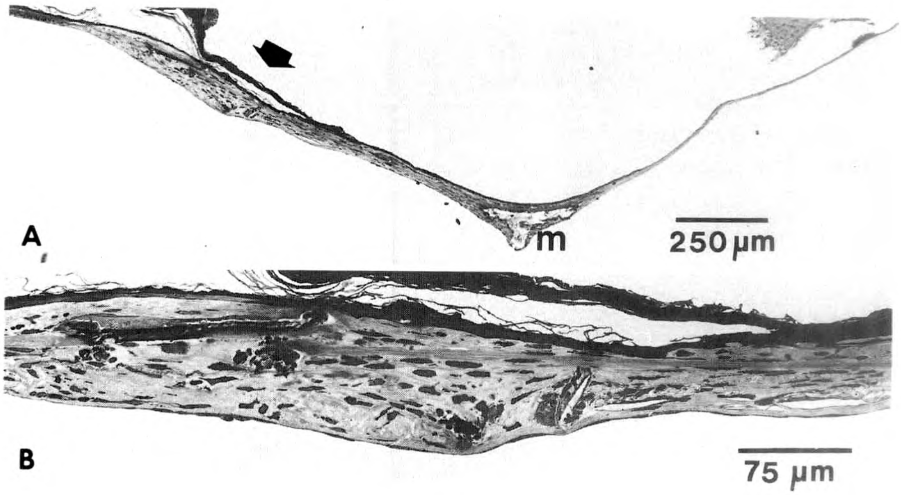

Fig 3. Light micrographs of pars tensa from PnC-infected ear 12 days after myringotomy. A) Toluidine blue, original ×60. Arrow — healed side of pars tensa, m — handle of malleus. B) Healed side at higher magnification (toluidine blue, original ×230).

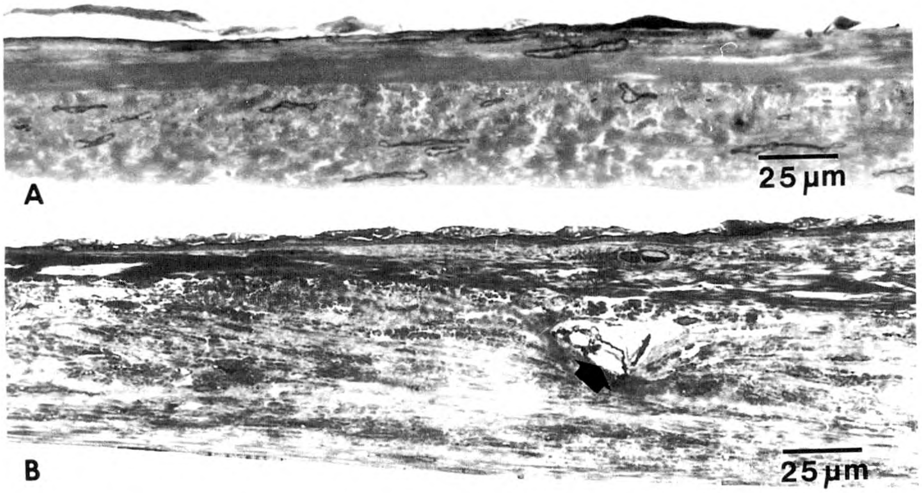

Fig 4. Light micrographs of pars tensa 6 months after PnC infection and myringotomy (toluidine blue, original ×460). A) Connective tissue layer is thickened. B) Bone formation is seen in thickened stroma (arrow).

Eight days after myringotomy the perforations had diminished considerably, although persisting in all cases. Sclerosis formation was present in all TMs.

Twelve days after myringotomy all control ears had healed, with sclerosis formation prevailing in the area around the malleus handle and the lateral borders of the TM. Vessels were dilated along the handle of the malleus.

At 3 and 6 months after myringotomy, all TMs appeared completely normalized, without scar formation or sclerosis.

Histopathologic Findings. On day 4, the pars tensa was edematous and there was pronounced proliferation of the keratinizing epithelium at the perforation edges. Polymorphonuclear neutrophils were present in the stroma. Exudate containing PMNs and macrophages was found on the inner surface of the TM. The inner epithelium was normal. The pars tensa was completely normal at sites in which no perforation had been performed. The pars flaccida was slightly edematous and vessels were dilated. The outer epithelium was thicker than normal. Parts of the inner epithelium were cuboidal.

On the 12th (Fig 6) day after myringotomy, the perforations had healed. The keratinizing epithelium was thicker than normal. Islands of keratinizing epithelium were seen in the stroma of the TM. The inner epithelium was normal. The pars tensa was completely normal at sites where no perforation had been performed. The pars flaccida was slightly edematous and the mast cells were degranulated. Polymorphonuclear neutrophils were present in the stroma. The outer epithelium was slightly thickened. The inner epithelium was normal.

At 3 and 6 months (Fig 7) the pars flaccida was completely normalized. At the perforation site, the pars tensa was slightly thinner than on the nonperforated side (3 µm versus 4 to 5 µm), but no other changes were observed with the light or electron microscope.

INFECTED EARS WITHOUT MYRINGOTOMY

Otomicroscopic Findings. Three days after the inoculation there was manifest AOM. By day 7 there was purulent effusion located medial to the pars flaccida in half of the animals. In the other half the infection had resolved but vessels were still dilated in the pars flaccida and along the handle of the malleus. By day 12, all TMs were normalized, and they remained so at 2 and 6 months.

Histopathologic Findings. In PnC-infected ears, the pars tensa was slightly thickened 4 days after inoculation. Polymorphonuclear neutrophils were seen along the inner epithelium, but no PMNs were seen in the connective tissue. The vessels of the pars flaccida were extremely dilated and the thickness was increased. Polymorphonuclear neutrophils and macrophages were seen in the connective tissue, and in some sections the outer and inner epithelia were thickened.

At day 12, the pars tensa was still thickened. No PMNs infiltrated the stroma. A prominent reaction was seen in the pars flaccida; the stroma was thickened with dilated vessels and macrophages. The outer epithelium was thickened and the inner epithelium was stratified with large epithelial cells.

By 2 and 6 months, the TMs had completely normalized without any persisting changes. The thickness of the pars tensa was 4 µm at 6 months.

DISCUSSION

Several clinical investigations have focused on the treatment of AOM with myringotomy. In a total of

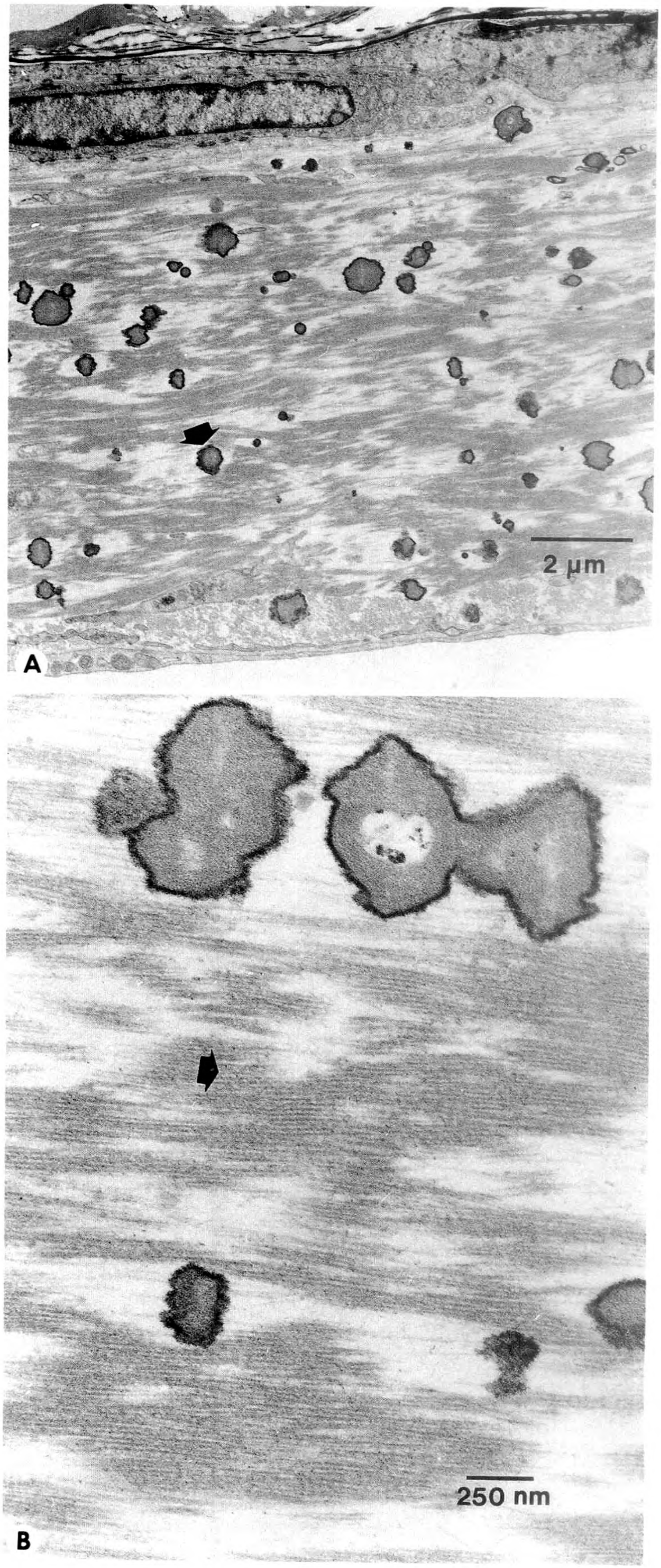

Fig 5. Electron micrographs of pars tensa 6 months after PnC infection and myringotomy. A) Sclerotic plaques (arrow) are spread in stroma (original ×8,000). B) Same specimen at higher magnification (original, ×40,000). Disorganized collagen layer constitutes stroma (arrow).

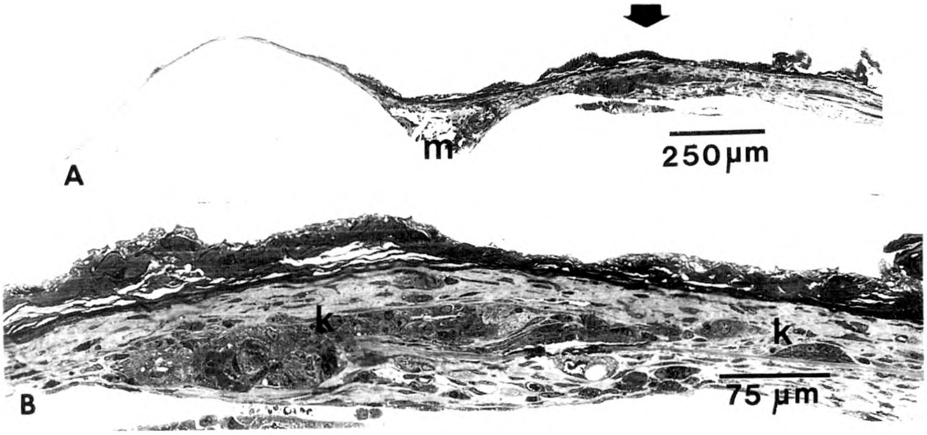

Fig 6. Light micrographs of noninfected pars tensa 12 days after myringotomy. A) Handle of malleus (m) centrally and healed side of pars tensa (arrow) are indicated (toluidine blue, original ×60). B) Healed side at higher magnification (toluidine blue, original ×230). Note islands of keratinizing epithelium (k) in stroma.

536 children, Kaleida et al[20] evaluated the effects of amoxicillin and myringotomy on the resolution of AOM. Their data provide no support for the routine use of myringotomy. Lidén et al[21] studied the use of oral antibiotics versus oral antibiotics plus myringotomy in the treatment of early recurrence of AOM in 79 children. No differences were found between the groups concerning healing rate or recurrence of otitis media in the short term or within 5 months, nor was there a difference in the persistence of secretory

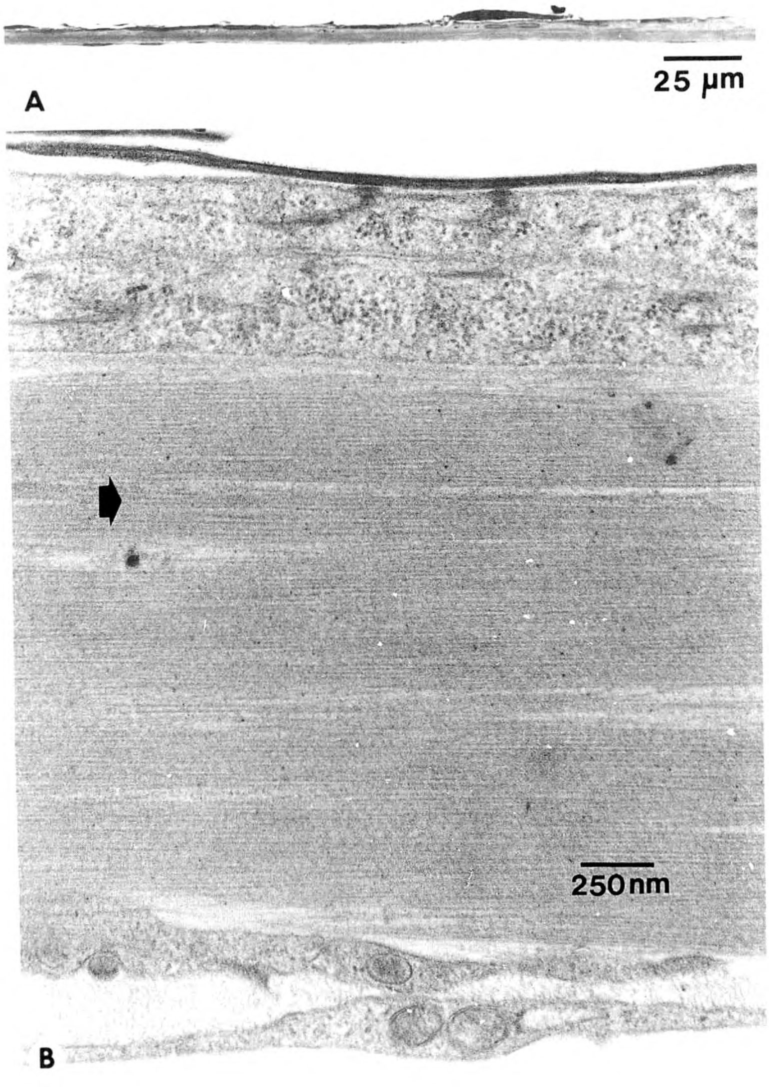

Fig 7. Noninfected pars tensa 6 months after myringotomy. A) Light micrograph (toluidine blue, original ×460). Tympanic membrane is normal. B) Electron micrograph (original ×40,000). Collagen fibers are lying parallel to each other (arrow).

otitis media (SOM) or healing of SOM. They concluded that myringotomy is of limited value in the treatment of an early recurrence of AOM. Van Buchem et al[22] evaluated the use of antibiotics, myringotomy, and symptomatic treatment of 171 children with AOM. No significant differences were found between the children treated only symptomatically and those who were myringotomized or treated with antibiotics. These authors[20-22] agree, however, that myringotomy is an appropriate treatment in selected cases such as for children with severe otalgia, children who fail to respond to antimicrobial treatment, and children in whom a suppurative complication develops.

On the other hand, Puhakka et al[8] reported that myringotomy in combination with antibiotics clearly accelerated recovery from AOM, compared with antibiotic treatment alone. They stated that myringotomy need not be carried out in mild cases of AOM but should always be performed in cases of recurrent AOM. In addition, Qvarnberg[9] reported that myringotomy at an early stage of AOM shortened the period of recovery and reduced the number of patients developing SOM. The Finnish Consensus Conference[10] concluded that myringotomy and aspiration of middle ear effusion is indicated in 1) children with distressing symptoms of AOM, 2) severely ill children, 3) infants less than 3 months of age, 4) immunologically compromised children, 5) patients with suppurative complications of AOM, 6) patients in whom response to antimicrobial therapy is unsatisfactory, 7) patients in whom accurate microbiological diagnosis is considered mandatory, and 8) certain cases of suspected AOM to verify the presence or absence of middle ear effusion. Also supporting the use of myringotomy is the increasing resistance of PnC to antibiotic treatment reported from several areas, which must be considered before rejecting myringotomy as a treatment method.[23-25]

In the present experimental study, more pronounced changes and a slower normalization of the TM were found in myringotomized PnC-infected ears than in myringotomized healthy ears. Of interest, perforations in infected ears closed more rapidly than in noninfected ears. In some cases, the perforation had closed even before the resolution of the infection, resulting in a purulent effusion medial to an intact TM. The noninfected TMs were affected by sclerosis formation early in the healing process following myringotomy, in contrast to the infected ears, in which only a few TMs were affected at this time. On the other hand, after 6 months, sclerosis formation was observed only among the TMs that had been infected. The noninfected TMs had normalized both otomicroscopically and histologically.

There was a slower resolution of the PnC infection of the myringotomized ears compared to PnC-infected ears in which myringotomy was not performed. The histologic study revealed that myringotomized PnC-infected TMs healed with a persisting thickened and disorganized collagen layer. In PnC-infected ears without myringotomy there were no histologic signs of scar formation 2 months after the inoculation. This suggests that the combination of infection and myringotomy is the cause of the longstanding structural changes in the TM.

Human and rat TMs show many similarities in architecture.[26] The rat middle ear anatomy and physiology are comparable to human conditions and therefore the rat may very well be used for AOM studies. The pneumococcal AOM model of the Sprague-Dawley rat has been extensively studied by us.[11,18,19,27] We are convinced that a comparison between the present experimental data and the previous results of TM structures during pneumococcal AOM that were not myringotomized[11,19] is accurate. The experimental conditions of both studies were the same and the bacterial inoculum was thoroughly standardized.[28]

During pneumococcal otitis media in the gerbil, irregularities in TM stiffness were investigated by moire interferometry.[29] A decrease in the TM stiffness was found from days 1 to 4. The reduction in TM stiffness during pneumococcal otitis media is probably caused by damaged fiber bundles in the lamina propria. The TM varies in stiffness from one portion to another, and "weak spots" were found midway between the annulus and umbo in the inferior part of the pars tensa. On one occasion, the TM was seen to rupture at this site during the measurements. Structurally, this region has a less-developed inner circular fiber layer, compared with other regions. The modified collagen structure seen at the myringotomized site of PnC-infected TMs in the present experiment may be responsible for such weak spots. It was recently shown by Sadé[30] that atelectatic TMs from human patients had a damaged collagenous layer in the pars tensa. Round cells, mostly lymphocytes and plasma cells, were present in the lamina propria. Sadé states that the atelectatic portion of the pars tensa is less rigid because of an impaired collagenous layer that in turn is secondary to an inflammatory process in addition to the effect of a prolonged negative middle ear pressure. We suggest from the present experiment that scar formation and impairment of the collagenous layer after myringotomy represent presumptive sites for retraction pockets and perforation in the pars tensa of the atelectasis-prone middle ear.

On the basis of the present experimental investigation, we conclude that myringotomy performed on

PnC-infected TMs results in a slower resolution of the infection and causes persistent changes in the collagen structure of the TM in the rat. Transferred to the clinical situation, this finding supports the view that myringotomy should be restricted and not be used routinely in AOM cases.

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IMAGING CASE STUDY OF THE MONTH

RADIOLOGIC FINDINGS IN A CARCINOMA-ASSOCIATED LARYNGOCELE

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INTRODUCTION

The recent literature has suggested that an association exists between laryngoceles and carcinoma of the larynx. We describe a case in which both lesions were identified radiographically and confirmed pathologically on surgical exploration.

CASE REPORT

A 74-year-old man with a 2-year history of T1N0M0 infiltrating squamous cell carcinoma of the right true vocal cord, previously treated with full-course radiotherapy, presented with increasing hoarseness of 1 month. The patient had done well following completion of radiotherapy. Physical examination revealed a severely hoarse but nonstridorous elderly man in no apparent distress. The nasopharynx and oropharynx were unremarkable. The larynx was erythematous and the right true vocal cord was fixed, with mucosal ulceration. The neck had approximately three small right high jugular (level 2) lymph nodes that were firm, mobile, and nontender. There were no other palpable neck masses, and the remainder of the findings on head and neck examination were unremarkable.

Radiographic evaluation was undertaken with magnetic resonance imaging (MRI). An axial T1-weighted image (T1WI) showed thickening of the right true vocal cord (Fig 1A), consistent with a neoplastic process. The abnormal signal intensity in this region extended across the midline at the anterior commissure, and there was also irregularity of the right thyroid cartilage, suggestive of invasion. At the supraglottic level, an axial T1WI showed a second mass lesion (which was nonenhancing) in the right paraglottic region (Fig 1B). This same lesion displayed a homogeneously high signal intensity (similar to cerebrospinal fluid) on a T2-weighted image (T2WI; Fig 1C). Figure 2 is a coronal T1WI, again focusing on the second lesion. Together, the images in Figs 1 and 2 suggested an internal laryngocele with a narrowing at the region of the ventricle, but necrotic supraglottic extension of a tumor could not be excluded. Figure 3 is a T2WI of the vocal cord lesion, and it is apparent that the tissue intensities of the paraglottic and glottic lesions are different on a T2WI, suggesting two distinct entities. Panendoscopy and biopsy showed recurrent squamous cell carcinoma of the right true vocal cord, and the patient was admitted for a total laryngectomy and a right radical neck dissection.

Gross examination of the larynx revealed an ulcerated lesion in the glottic area, measuring 2.5 x 2.0 cm. This lesion involved the right anterior true vocal cord and extended 1.5 cm superiorly to involve the right ventricle, false vocal cord, and lower epiglottic tissue. When the lesion was cross-sectioned, a firm white-tan area with a maximal depth of 5 mm was noted. A right laryngocele measuring 2.0 x 1.5 x 1.5 cm was identified and opened to reveal thick mucoid material.

Microscopic examination of the surgical specimen identified an infiltrating, moderately differentiated squamous cell carcinoma of the right true vocal cord with focal extension across the midline, involving the left anterior true vocal cord. All resected nodes and margins were negative for tumor. A laryngocele was confirmed on the right.

DISCUSSION

A laryngocele is a dilatation or herniation of the laryngeal saccule above the superior margin of the thyroid cartilage.[1] The saccule is a narrow, blind pouch arising from the anterior end of the laryngeal

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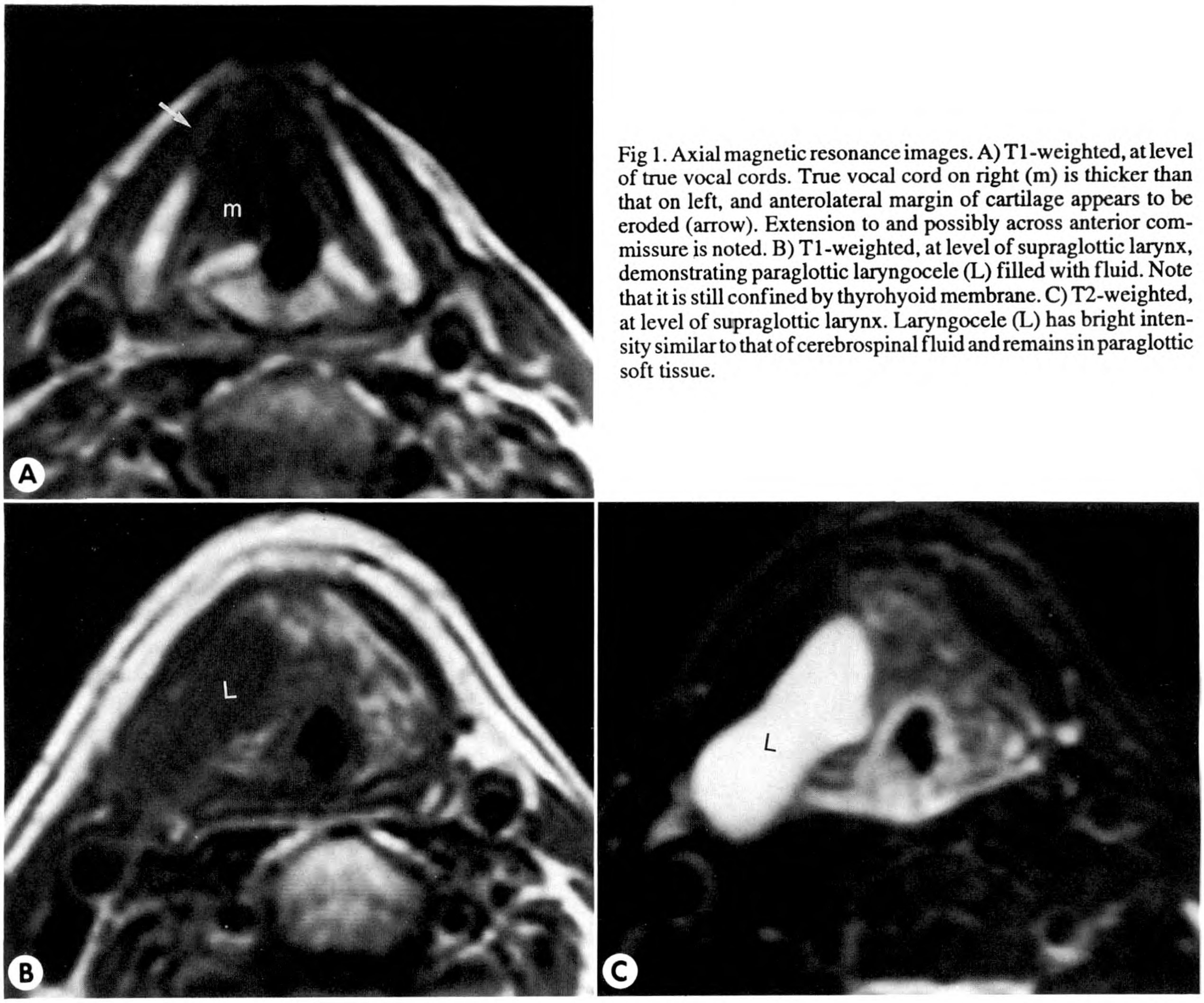

Fig 1. Axial magnetic resonance images. A) T1-weighted, at level of true vocal cords. True vocal cord on right (m) is thicker than that on left, and anterolateral margin of cartilage appears to be eroded (arrow). Extension to and possibly across anterior commissure is noted. B) T1-weighted, at level of supraglottic larynx, demonstrating paraglottic laryngocele (L) filled with fluid. Note that it is still confined by thyrohyoid membrane. C) T2-weighted, at level of supraglottic larynx. Laryngocele (L) has bright intensity similar to that of cerebrospinal fluid and remains in paraglottic soft tissue.

ventricle, and extends superiorly in the paralaryngeal space, bounded by the false vocal cord medially and the thyroid cartilage laterally. This structure is highly variable in size, and ranges from being absent to extending 15 mm or more into the aryepiglottic fold.[2] The laryngocele, like the saccule and ventricle, is lined with pseudostratified ciliated columnar epithelium containing numerous goblet cells.

There are three types of laryngoceles: internal, external, and mixed. An internal laryngocele is formed when the saccule dilates but remains within the soft tissue of the laryngeal wall. Although it may extend as high up as the epiglottis or tongue base, it does not penetrate the thyrohyoid membrane. The external laryngocele, on the other hand, is an extralaryngeal dilated pouch that has penetrated through the thyrohyoid membrane but remains connected to the ventricle via a nondilated segment of the intralaryngeal saccule. A mixed laryngocele includes both internal and external dilatations of the saccule.

The pathogenesis of laryngoceles is uncertain. Some feel there is a congenital predisposition, owing to the embryological development of the saccule. Following a period of rapid growth during the second month of embryogenesis, the saccule's rate of growth progressively slows in comparison to the rest of the larynx. The timing of these events varies among individuals, resulting in a random distribution of congenitally long saccules. A congenitally long saccule is the underlying condition felt most likely to influence future laryngocele development.[2]

Another theory suggests that increased intralaryngeal pressure leads to the dilatation or herniation of the saccule. This theory is supported by the prevalence of laryngoceles in patients of certain occupations such as glass blowers and wind instrument players, and those with chronic respiratory disease (secondary to increased coughing). Although this theory is more widely accepted, some authors note that it is not exclusive of, and can easily accommodate, the theory of congenital predisposition to laryngoceles; ie, those who are congenitally predis-

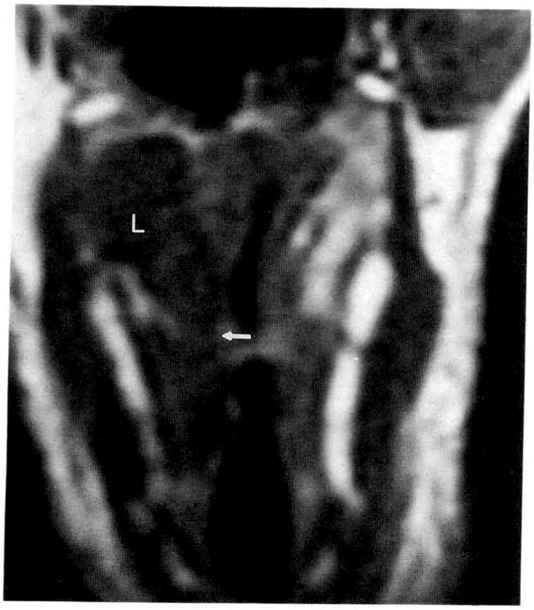

Fig 2. Coronal T1-weighted magnetic resonance image shows internal laryngocele (L) in paraglottic tissues extending to point (arrow) at ventricular level. True vocal cord on right is thicker than that on left, and squamous cell carcinoma has obstructed saccule of ventricle.

posed may develop laryngoceles with prolonged exposure to increased intralaryngeal pressure.[2]

Laryngoceles are relatively rare; the incidence of asymptomatic laryngoceles is reported as being 4.2% to 12.5%.[1] These findings are based on observation of patients undergoing computed tomography (CT) of the head and neck for a variety of primary otolaryngological diseases other than laryngocele, whereupon a laryngocele was identified. There may be an association with laryngeal carcinoma.

In a review of the literature, Celin et al[3] reported an incidence of laryngoceles concurrent with squamous cell carcinoma of the larynx of 4.9% to 28.8%. Close et al[1] reported that among 59 patients with biopsy-proven squamous cell carcinoma of the larynx, 17 (28.8%) had an associated laryngocele, whereas 21 laryngoceles were identified among 245 patients (8.6%) without laryngeal cancer. From another perspective, 45% of patients with laryngoceles had proven laryngeal cancer,[1] in close agreement with the report given by Lindell et al,[4] who observed 49% of laryngoceles to be associated with laryngeal carcinoma.

The clinical presentation and diagnosis of laryngoceles has changed dramatically in the last 15 years. Whereas most laryngoceles had been diagnosed clinically in symptomatic patients, advances in radiology now provide early identification of asymptomatic laryngoceles, which account for the majority of these lesions. Close et al,[1] in their report of 305 patients undergoing neck CT, found 39 cases of laryngocele, of which 38 were asymptomatic. Laryngoceles diagnosed among 2,068 patients reported by Lindell et al[4] were asymptomatic, associated findings on radiographic analysis for suspected laryngeal or hypopharyngeal cancer. When laryngoceles are symptomatic, manifestations depend on the site of involvement. Internal laryngoceles manifest with hoarseness, dyspnea, cough, and mass sensation. External laryngoceles present as a soft, reducible neck mass that enlarges with increased intralaryngeal pressure.[2,4] Compression of the mass may elicit gurgling and hissing sounds, which has been referred to as Bryce's sign.[5]

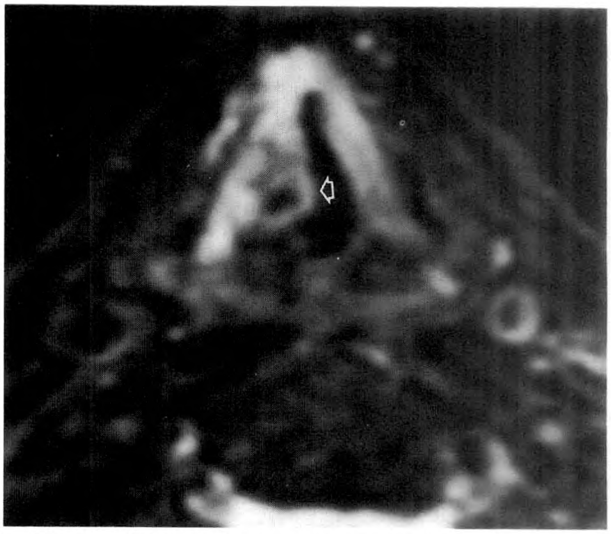

Fig 3. Axial T2-weighted magnetic resonance image at level of true vocal cords. Note difference between intensity of tumor (arrow) on this image and that of fluid-filled laryngocele in Fig 1C.

As briefly alluded to above, radiography contributes enormously to the diagnosis of these lesions. Previously, plain radiographs, linear tomography, and contrast laryngography were the studies of choice.[4,6] In the uncomplicated air-filled laryngocele, the combination of an air-filled region confined by soft tissue and ossified cartilage is an easy diagnosis. However, when the air is replaced with mucus or pus to form laryngomucoceles and laryngopyoceles, respectively, diagnosis is more difficult. In these cases, CT has proven valuable.

Through cross-sectional imaging and superior contrast resolution, the CT scan has become an integral study for the evaluation of laryngeal lesions. As already noted, laryngoceles may be air- or fluid-filled. Not only is CT able to detect a fluid-filled lesion, it can also predict the nature of the fluid based on attenuation intensities, which range from near-water density to soft tissue density. Thus, the CT appearance of a well-defined structure of air or near-water density in a characteristic location suggests laryngocele. When the lesion is of soft tissue density, its location and a smooth surface on CT along with a normal mucosal appearance on laryngoscopy suggest laryngocele.[7] Close et al[1] employed CT in their prospective analysis and diagnosis of laryngoceles, and concluded that CT was highly sensitive for the detection of laryngoceles, both symptomatic and asymptomatic. Furthermore, they found CT to be more sensitive than clinical symptoms and laryngoscopy in detecting laryngoceles.

Radiographic evaluation of the present case consisted of MRI, which proved useful in identifying both lesions. T1-weighted imaging revealed the right vocal cord neoplasm with cartilaginous invasion and possible extension across the midline (appearing as a mucosal thickening in Fig 1A), and it also demonstrated a hypointense fluid-filled lesion in Fig 1B. Additional imaging of the second lesion using a T2WI (Fig 1C) revealed a fluid-filled collection internal to the thyrohyoid membrane, suggesting an internal laryngocele. A T1WI in the coronal plane (Fig 2) estimated the vertical extent of the laryngocele and suggested its location relative to the vocal cord neoplasm. Figure 3 is a T2WI at the level of the vocal cords, demonstrating the right vocal cord neoplasm, and its different intensity when compared to the laryngocele.

This report has demonstrated the utility of MRI in the radiographic workup of a laryngocele. Because of its multiplanar capability and superior soft tissue resolution when compared with other imaging modalities, MRI is an ideal method of noninvasive assessment of soft tissue lesions. In the present case, MRI accurately depicted the vocal cord lesion and the extent of the laryngocele. Furthermore, given the known association between laryngeal carcinoma and laryngoceles, it is important that tumor involvement of an associated laryngocele be determined so that an appropriate surgical resection can be carried out. One report found that a preoperative CT scan was unable to differentiate between tumor and mucus within a laryngocele, but an MRI was able to identify its contents as tumor.[3] Although we did not employ CT in our assessment, we too believe that for the above reasons, MRI is of considerable benefit in the diagnosis and preoperative evaluation of laryngoceles.

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CLINICOPATHOLOGICAL CONSULTATION

MUCOSAL ADENOID SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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Adenoid squamous cell carcinoma is an uncommon variant of squamous cell carcinoma. The lesion is histologically distinctive and it is usually localized on the skin of the head and neck region; it only rarely involves the mucosal sites. The differential diagnoses include adenosquamous carcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, basaloid squamous cell carcinoma, and metastatic adenocarcinoma. Surgery is the treatment of choice. The biologic behavior of this neoplasm is more aggressive when it involves mucosal areas, and the prognosis seems worse than that of conventional squamous cell carcinoma.

Adenoid squamous cell carcinoma (ASCC) is an uncommon, histologically distinctive variant of squamous cell carcinoma (SCC) of the skin (and especially of the sun-exposed areas) and was first recognized as a distinctive entity by Lever[1] in 1947. It is predominantly encountered on the skin of the head and neck region and only rarely has been observed in mucosal sites such as lip[2-6] — in particular on the vermilion of the lower lip[3-6] — oral cavity,[7,8] nasopharynx,[9] tongue,[10] sinonasal tract,[11] hypopharynx,[11] larynx,[12] and vulva.[13,14] Therefore, there are cutaneous and mucosal counterparts of this malignancy. We will discuss only the rarer mucosal counterpart.

This tumor has been reported under various names, eg, adenoacanthoma, pseudoglandular SCC, acantholytic SCC, and SCC with glandlike (adenoid) features.

The World Health Organization classification describes this neoplasm as "a squamous cell carcinoma in which pseudoglandular spaces or lumina are present. The pseudoglandular structure in this variant of squamous cell carcinoma results from acantholysis of the tumor cells. There is no evidence of true glandular differentiation or mucin production."[15(p31)]

Usually, the tumor is considered as a variant of SCC, but Yanagawa et al[16] suggest that it derives from minor salivary glands as a consequence of squamous metaplasia occurring in glandular tissue. Macroscopically, the lesion appears as a nonulcerated mass. Histologically, it resembles the usual SCCs, but shows acantholysis of the malignant squamous cells, producing pseudolumina that mimic glandular differentiation (see Figure, A-C). This acantholytic change appears to begin in the basal layer of the squamous epithelium. Areas of dysplasia are sometimes seen in the accompanying surface epithelium. Clear and spindle cells may be present (see Figure, D,E). A desmoplastic reaction may be an accessory finding. A chronic inflammatory infiltrate and a basophilic degeneration of collagen are usually present in the stroma (see Figure, F).

Periodic acid–Schiff reaction for glycogen may demonstrate focal staining. Mucicarmine and Alcian blue stains for mucin are negative. Immunohistochemically, ASCC is positive for cytokeratin, epithelial membrane antigen, and carcinoembryonic antigen and may express vimentin. Electron microscopy shows polygonal and oval cells with desmosomes, scattered intracellular tonofilaments, and microvilli. The neoplastic cells surrounding the pseudolumina show defective cohesion and lack appreciable evidence of glandular differentiation.

The criteria for diagnosing ASCC are as follows.

1. A conventional SCC component (usually well

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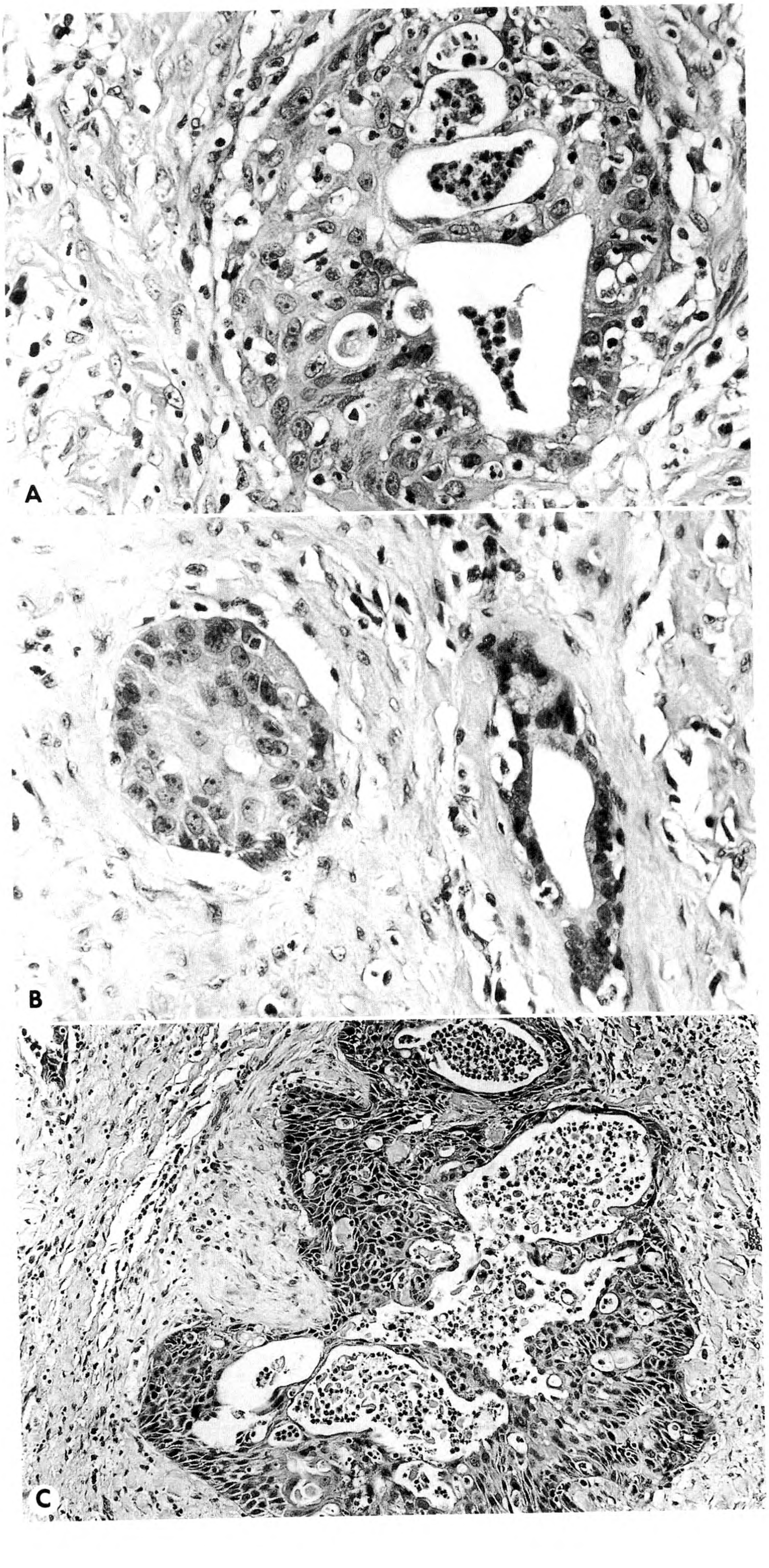
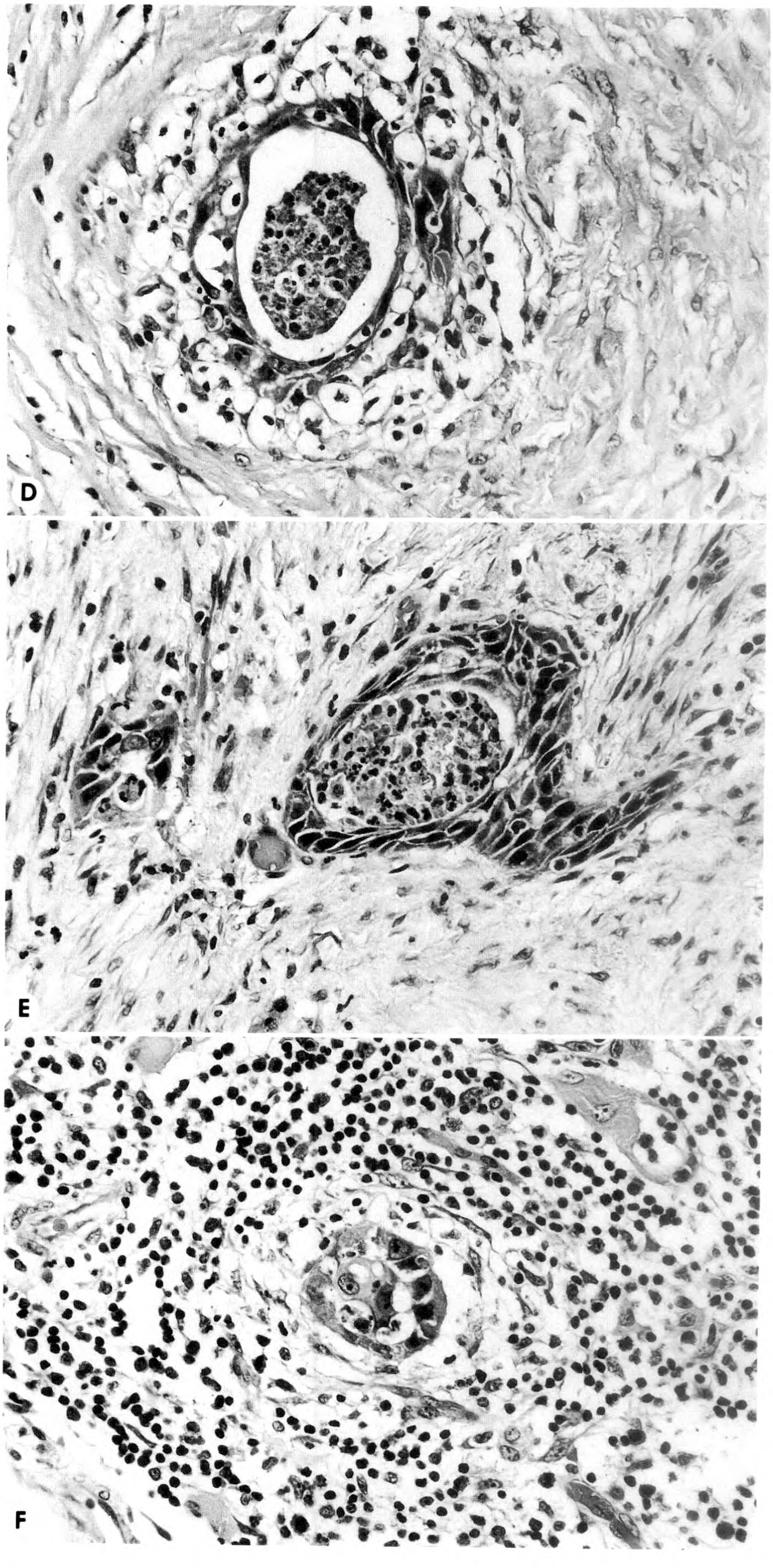


Adenoid squamous cell carcinoma of larynx. A) Typical adenoid pattern of tumor. B) In this area, lesion could be confused with adenosquamous carcinoma, but mucicarmine staining is negative in adenoid squamous cell carcinoma. C) Pseudolumina containing dyskeratotic acantholytic cells. (Continued on next page.)



(Continued) D) Many clear cells are present. E) Typical pattern. Note presence of spindle cells in stroma. F) Neoplastic cells are surrounded by large number of inflammatory cells.

TABLE 1. COMPARISON OF PATHOLOGIC FINDINGS BETWEEN ADENOID SQUAMOUS CELL CARCINOMA AND ADENOSQUAMOUS CARCINOMA

Features	*Adenoid Squamous Cell Carcinoma*	*Adenosquamous Carcinoma*
Acantholysis	Present	Absent
Glandular structures	Absent	Present
Mucicarmine	Negative	Positive
Perineural infiltration	Usually absent	Frequent
Chronic inflammatory infiltration	Usually present	Absent

TABLE 2. COMPARISON OF PATHOLOGIC FINDINGS BETWEEN ADENOID SQUAMOUS CELL CARCINOMA AND ADENOID CYSTIC CARCINOMA

Features	*Adenoid Squamous Cell Carcinoma*	*Adenoid Cystic Carcinoma*
Acantholysis	Present	Absent
Perineural infiltration	Usually absent	Prominent
Chronic inflammatory infiltration	Usually present	Absent
Clear cells	Present	Absent
Squamous component	Present	Absent

differentiated) is present on the surface of the neoplasm.

2. Pseudolumina containing single or grouped acantholytic and dyskeratotic epithelial cells or cellular debris are present under the squamous neoplastic component and comprise all the neoplasm. This nonsolid component usually shows an alveolar pattern or a pseudoglandular arrangement. Some pseudolumina are empty.
3. Clear cells are usually present.
4. A chronic inflammatory infiltrate is common.
5. Spindle cells and a desmoplastic reaction may also be present.

The differential diagnosis includes adenosquamous carcinoma (ASC), adenoid cystic carcinoma (ACC), mucoepidermoid carcinoma (MC), basaloid squamous cell carcinoma (BSCC), and metastatic adenocarcinoma.

Adenosquamous carcinoma demonstrates, in addition to a squamous component, true separate foci of adenocarcinoma. The latter is not seen in ASCC. Acantholysis is absent in ASC and is present in ASCC. Stains for epithelial mucin are strongly positive in ASC and negative in ASCC. Furthermore, chronic inflammatory infiltration is usually absent in ASC, while it is present in ASCC. Table 1 summarizes some differential pathologic aspects of the two tumors.

Acantholysis, chronic inflammatory infiltration of the stroma, and clear cells are not features of ACC, while perineural infiltration is often prominent in this tumor (Table 2).

The presence of vacuolated mucin-producing cells and true glandular structures in MC distinguishes that lesion from ASCC[12] (Table 3). The mucin staining is somewhat difficult to interpret, because it seems to be associated with carcinoma extending into salivary ducts. It is conceivable that the mucin-positive cells are related to residual mucocytes (Carol F. Adair, personal communication, 1994).

Distinct palisading of rectangular tumor cells at the peripheries of islands of tumor cells, producing a basaloid pattern, is not a feature of ASCC, while it is constant in BSCC. The metastatic adenocarcinoma shows true glandular features, while ASCC produces pseudolumina that mimic glandular differentiation and exhibits predominant squamous differentiation.

The nonmucosal ASCC should be differentiated also from angiosarcoma of the skin. Appropriate immunohistochemical studies are very useful in differentiating the two lesions,[17] although it should be borne in mind that some angiosarcomas — particularly those with an epithelioid character on light microscopy — may exhibit focal cytokeratin positivity (an observation that underscores the value of employing panels of antibodies, rather than single

TABLE 3. COMPARISON OF PATHOLOGIC FINDINGS BETWEEN ADENOID SQUAMOUS CELL CARCINOMA AND MUCOEPIDERMOID CARCINOMA

Features	*Adenoid Squamous Cell Carcinoma*	*Mucoepidermoid Carcinoma*
Mucin-producing cells	Absent	Present
True glandular structures	Absent	Present
Carcinomatous changes in surface mucosal epithelium	Present	Absent
Squamous carcinoma component	Nearly always well differentiated	Almost never keratinizes

antibodies, to refine a differential diagnosis with the aid of immunohistochemistry).[18]

Surgery is the treatment of choice for ASCC of the head and neck. Unlike ASCC of the skin, this tumor is associated with aggressive behavior and a poor prognosis when it occurs in the mucosa of the upper aerodigestive tract.[9] Regional lymph node metastases have been reported by some authors.[7,9,10] Batsakis and Huser[11] believe that mucosal head and neck ASCCs have a worse prognosis than conventional SCCs.

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EPITHELIAL HYPERPLASTIC LESIONS OF THE LARYNX

The International Conference on Epithelial Hyperplastic Lesions of the Larynx will be held October 28-30, 1996, in Ljubljana, Slovenia. For more information, contact Bostjan Luzar, MD, or Aleksandar Vodovnik, MD, Institute of Pathology, Korytkova 2, 61105 Ljubljana, Slovenia; telephone 386 61 1403042 (Int. 268); fax 386 61 301 816; E-mail Vodovnik@IBMI.MF.UNI-LJ.SI.

Immunobiology in Otorhinolaryngology. Progress of a Decade

Goro Mogi, Jan E. Veldman, and Hideyuki Kawauchi, editors. Hard cover, illustrated, indexed, 669 pages, 1994. Kugler Publications, New York, NY, $206.

This volume consists of a collection of papers from the International Academic Conference on Immunobiology in Otology, Rhinology, and Laryngology. This conference was held in Oita, Japan, in April 1994. Besides the specific studies of the ear, nose, throat, head, and neck, there were five special lectures in the field of immunology. As is typical with proceedings books, each presentation is concise and consists of an introduction, material and methods, results, and discussion.

As expected, the pathogenesis of otitis media with effusion and its associated immunologic factors is a subject well covered.

There are several conditions (Meniere's disease, sudden idiopathic sensorineural hearing loss, progressive congenital sensorineural hearing loss) for which steroids, in some cases, improve the hearing. In fact, there are reports of improved hearing with steroids in which there is no known underlying autoimmune disease (or evidence of elevated immune complexes such as erythrocyte sedimentation, etc). Typically, in such cases (non-autoimmune diagnosis), there are reports of steroid-responsive sensorineural hearing loss in 50% of cases examined. One report stated that a case of hearing loss caused by aortitis syndrome (Takayasu's disease) was steroid-responsive and deteriorated whenever prednisolone administration was stopped and improved upon re-administration (Kanzaki J, Ino T, Takahashi M, et al. Clinical Investigations on Fluctuating Hearing Loss Without Vertigo [in Japanese]. *Audiology (Japan)* 1975;18:88-98). At present there are no reliable diagnostic tests for steroid-responsive sensorineural hearing loss. Several interesting papers in this book address this problem.

The immunohistochemistry of nasal mucosal allergic response is very involved and addressed by many studies. In general, clinical manifestations result from a chain of pathophysiological events initiated by antigen-IgE interaction on the surface of mast cells, which degranulate, resulting in the liberation of such mediators as histamine and serotonin. Tissue edema is produced by vascular permeability caused by these amines.

There is a problem I have with proceedings books. These days, hundreds of papers can make up a volume such as this one. There is no subject index. It is then frustrating to try to find, for example, the use of prophylaxis with erythromycin in chronic sinusitis — one of the topics in this volume.

Each research presentation is well done and not a "how to do it" paper as is sometimes typical of a proceedings compilation. The volume is recommended to all physicians in our specialty, especially researchers, because this is an important and timely subject.

DENNIS G. PAPPAS, MD
Birmingham, Alabama

The Sinuses

Paul J. Donald, Jack L. Gluckman, and Dale H. Rice, editors. Hard cover, illustrated, indexed, 687 pages, 1994. Raven Press, New York, NY, $175.

This book has 18 contributing authors. The text is divided into five parts to include basic science, inflammatory diseases, trauma, neoplastic diseases, and related conditions and procedures.

Part 1 of the text included the first seven chapters and was an excellent and well-written review of the history of surgery for sinusitis, embryology, anatomy, physiology, microbiology, pathology, and radiology. The chapter on embryology was exceptionally well written and understandable for such a complicated subject. Dr Donald's opening paragraphs in chapter 3 are unfortunately true, that is, "the modern otolaryngologist, a victim of revisionist philosophy in modern basic medical education, begins specialty training with a rudimentary understanding of the head and neck anatomy." Overall, the first seven chapters of the book that cover basic science are well written, understandable, and extremely well illustrated.

Section 2 of the text covers inflammatory diseases and is inclusive of chapters 8 through 21. Again, this particular section of the book is well written and well illustrated; however, one chapter stood out as being particularly poor and is not only a blemish to this particular section of the book, but quite a noticeable blemish on the face of an otherwise good textbook. The chapter referred to is chapter 9, titled "Allergy in the Clinical Office," and there are several obvious errors of fact printed. To mention only a few, the author suggests that two IgE molecules attach themselves to antigen and *then* bind to a mast cell, resulting in degranulation, when in fact the IgE molecules are already attached to the mast cell before the antigen binds. Another glaring error is the assumption that the scratch test is an acceptable method of testing, when in fact the Council on Scientific Affairs of the American Medical Association published in JAMA, September 1987, that scratch tests are not a reproducible technique of testing and "are no longer recommended."

These two errors are so obvious that the reader would wonder if this particular chapter somehow escaped review by the editors, because they would have been obvious to them as well. Should there be a second edition of this book, chapter 9 should be rewritten. Chapters 10 and 11 were very interesting contrasts regarding the diagnosis and management of food-sensitive patients, and the comparisons were very interesting. The remaining chapters of this particular section on inflammatory diseases were, again, understandable, well written, and very clearly illustrated.

Part 3 of the text involves every aspect of trauma to the nose, the facial structures, and paranasal sinuses that could be imagined. It is absolutely superb in its presentation, explanation, and illustration and should be required reading for all residents. The final two sections of the book, Neoplastic Disease and Related Conditions and Procedures, were excellent, particularly chapter 32, which covered the differential diagnoses of facial pain. Again, this chapter in particular is "must" reading for any resident.

The editors set out to produce a definitive source of reliable and well-founded information related to sinus disease and they did accomplish that, with the exception of chapter 9, which does detract from the rest of the book. I would recommend this book for all residents in training, as well as any practitioner who performs nasal and paranasal sinus surgery. The textbook is comprehensive, well written, and well illustrated and would enhance the library of any practicing otolaryngologist.

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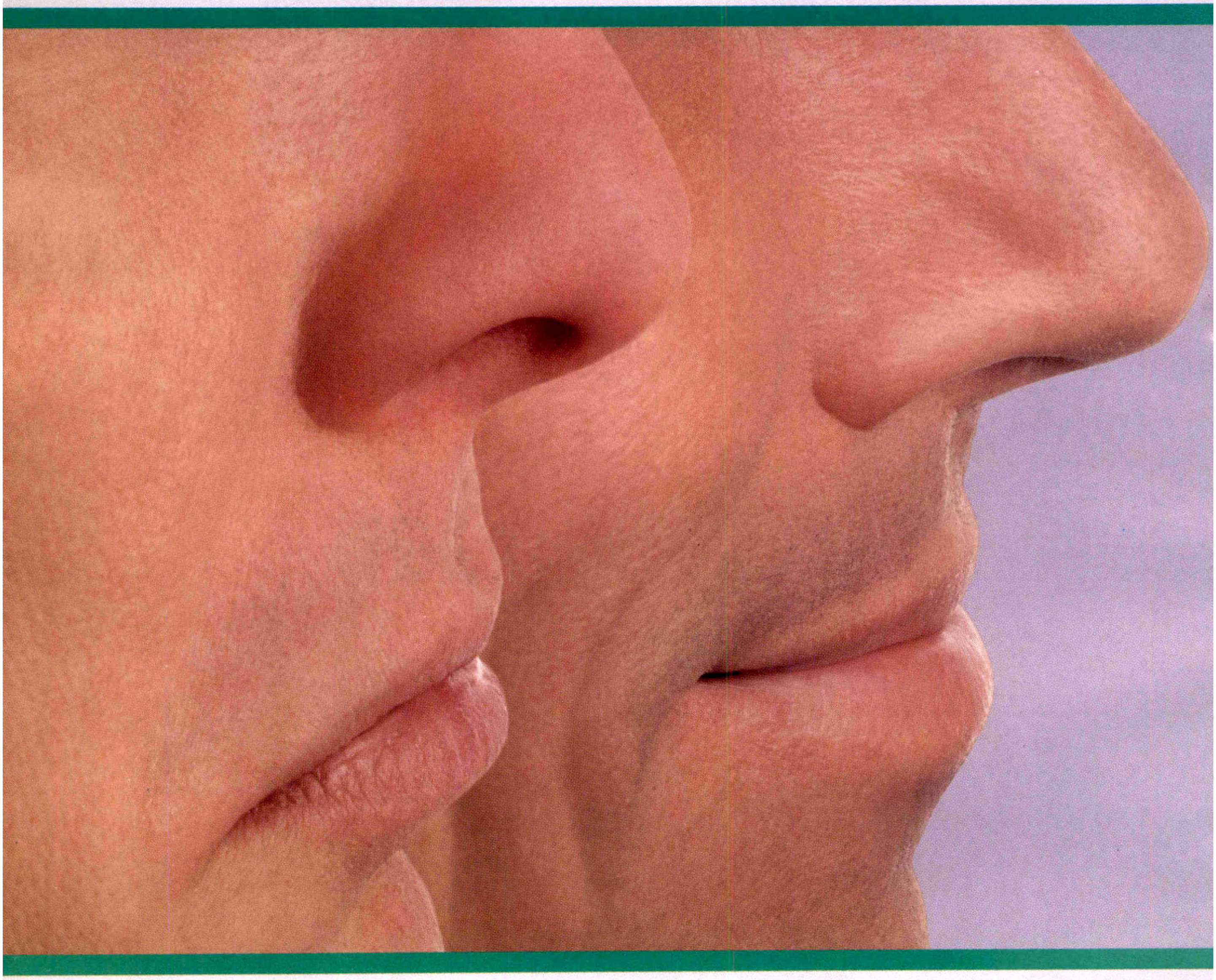

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MEASURING PATIENT BENEFIT FROM OTORHINOLARYNGOLOGICAL SURGERY AND THERAPY

KEN ROBINSON, PHD
STUART GATEHOUSE, PHD
GEORGE G. BROWNING, MD, FRCS
GLASGOW, SCOTLAND

The Glasgow Benefit Inventory (GBI) is a measure of patient benefit developed especially for otorhinolaryngological (ORL) interventions. Patient benefit is the change in health status resulting from health care intervention. The GBI was developed to be patient-oriented, to be maximally sensitive to ORL interventions, and to provide a common metric to compare benefit across different interventions. The GBI is an 18-item, postintervention questionnaire intended to be given to patients to fill in at home or in the outpatient clinic. In the first part of the paper, five different ORL interventions were retrospectively studied: middle ear surgery to improve hearing, provision of a cochlear implant, middle ear surgery to eradicate ear activity, rhinoplasty, and tonsillectomy. A criterion that was specific to the intervention was selected for each study, so that the patient outcome could be classified as above and below criterion. In all five interventions, the GBI was found to discriminate between above- and below-criterion outcomes. The second part of the paper reports on the results and implications of a factor analysis of patient responses. The factor structure was robust across the study, and so led to the construction of subscales. These subscales yield a profile score that provides information on the different types of patient benefit resulting from ORL interventions. The GBI is sensitive to the different ORL interventions, yet is sufficiently general to enable comparison between each pair of interventions. It provides a profile score, which enables further breakdown of results. As it provides a patient-oriented common metric, it is anticipated that the GBI will assist audit, research, and health policy planning.

KEY WORDS — health care outcome assessment, quality of life.

INTRODUCTION

An important requirement of contemporary medicine is the assessment of patient benefit or change in health status resulting from medical and surgical intervention, with particular emphasis on its measurement. Increasing accountability of the health service provider requires patient-oriented outcome measures, both for research to establish which treatments are effective, and for audit to establish whether treatment regimens based on research are being successfully implemented.

A useful measure of patient benefit from otorhinolaryngological (ORL) interventions must fulfill three requirements: it must be patient-oriented, be sensitive to the changes in health status resulting from the intervention, and enable comparison between different interventions. Patient-oriented measures are important because they provide a health consumer perspective that is becoming salient in the determination of health care policy. This is linked with political concerns, as health care provision becomes increasingly shaped by patients' needs and preferences.

The second requirement of a measure of patient benefit is that it must be sensitive to the changes in health status following the intervention. Many ORL interventions are effective but not lifesaving, and so traditional outcome measures such as mortality and morbidity may not be as informative as a patient-oriented measure that is maximally responsive to the intervention or interventions of interest.

The third requirement is generality; a patient benefit measure must enable comparison between different interventions. A common patient-oriented metric could then be used to supplement data on mortality, morbidity, and service utilization in informing health policy and planning. A patient-oriented measure would also be of use for audit purposes; it would help identify areas of particular expertise and weakness at personal, departmental, and regional levels. A further application for a common patient-oriented metric is in research. For example, it would be useful in a model that may potentially describe the relationship between patient benefit and preintervention variables such as patient personality, motivation, and expectations.

Existing measures of health status are available, and may be used as a quality-of-life measure following an ORL intervention. Several reviews of these measures have recently been published.[1-4] The aim of the health status measures is to enable cross-comparison among many health conditions, among different health interventions, and among demographic and

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cultural subgroups. However, there are practical limitations to some of the better-known measures. For example, the Sickness Impact Profile[5,6] is restricted in its use because it is primarily interviewer-administered, and comprises 136 items. The Nottingham Health Profile[7] has been extensively validated, is comparatively short at 38 questions, and is easy to complete. However, there is evidence that it is not responsive to common nonacute disorders that are surgically treated (eg, hemorrhoids, hernias, varicose veins, peptic ulcers, cysts, and polyps).[8] Its main application appears to be in comparing the health status of patients suffering from major conditions, rather than the effect of the health care interventions.[3] Another measure that shows promise is the Short Form-36,[9,10] but this as yet has not been convincingly shown to reflect health care interventions in a responsive fashion.[10,11]

A second approach is the use of a patient satisfaction questionnaire. Typically, these are measures that ask patients about the quality of hospital care based on the consideration and courtesy of the surgical and medical staff, and the adequacy of hospital services. As with all customer satisfaction scales, results are always affected by a positive bias.[12,13] Often patients are reluctant to say that they are unsatisfied, because they feel grateful for medical or surgical attention, even when the intervention is not technically successful. Because of this positive bias, it is difficult to find a measure of patient satisfaction that is sensitive to medical or surgical intervention.[12,13]

A third, and often used, approach is the use of disease-specific measures. These are technical measures of surgical success, as well as questionnaires developed to provide a symptom score associated with the disease. Technical measures have been routinely used to audit surgical series, but are specific to the surgical intervention. Similarly, symptom scores have also been used to measure outcome, but are specific to the disease that is being investigated. This lack of a common metric represents the chief drawback to this approach. Although mortality and morbidity figures have been used to compare interventions, a patient-oriented measure of benefit is likely to provide qualitatively different information.

A fourth approach is to develop a questionnaire that measures the change in health status resulting from different types of ORL interventions. As stated earlier, such a questionnaire must be patient-oriented, be maximally sensitive to the effect of the intervention, and be generalizable across different ORL interventions. Given that maximal sensitivity to change was critical, it was decided to directly ask about the change in health status resulting from surgery, rather than take preoperative and postoperative measures and subtract one from the other. The questions in the Glasgow Benefit Inventory (GBI) were generated to measure a change in health status, where health status is defined as the general perception of well-being, as well as total psychological, social, and physical well-being.[14]

The first part of the paper examines the sensitivity to change of the GBI. We studied five different ORL interventions, where the success of the intervention was measured by a criterion. This criterion is specific to each ORL intervention, and so it was used to divide patients into two groups: above and below criterion, which are more and less successful, respectively. Using this method, we investigated whether the GBI was sensitive to the change in health status resulting from ORL interventions. If the GBI has the propensity of being sensitive to change resulting from ORL interventions, then it should discriminate between the above- and below-criterion groups in all five interventions. Moreover, the demonstration that the GBI is applicable to a number of different ORL interventions provides a test of its generality. The second part of the paper investigated the factor structure of the GBI, and examines the implications of the factor structure for its scoring. Factor analysis is a multidimensional statistical technique that uses the pattern of patient responses, and reduces them to a number of underlying factors. These factors can then inform us of what the GBI actually measures, and provide the basis for the generation of benefit subscales.

PART I: SENSITIVITY TO CHANGE OF THE GBI

General Method. Five retrospective studies investigated the sensitivity to change of the GBI. There were five ORL interventions: 1) middle ear surgery aimed at improving hearing (stapedectomy, ossiculoplasty, and myringoplasty), 2) a cochlear implant aimed at improving hearing in the profoundly deaf, 3) middle ear surgery aimed at eradicating ear activity (primarily mastoid procedures), 4) nasal surgery aimed at improving symptoms of blockage and disfigurement (rhinoplasty), and 5) pharyngeal surgery aimed at alleviating chronic sore throat (tonsillectomy).

In the pilot phase of the study, 38 questions were generated that potentially reflected a change in health status resulting from an ORL intervention. These questions were based on previous interview of patients and of surgical staff, as well as a review of the literature. The questions covered aspects of general, psychological, social, and physical benefit from an ORL intervention. The response to each question was based on a five-point Likert scale ranging from a large change for the worse, to no change, to a large

Since your (intervention), do you have more or less self-confidence?

Much less self-confidence	Less self-confidence	No change	More self-confidence	Much more self-confidence
1	2	3	4	5

Fig 1. Sample item from Glasgow Benefit Inventory (GBI).

change for the better. A sample question is shown in Fig 1.

Following the pilot phase, 18 of the 38 questions were retained. The criteria were the exclusion of questions that resulted in patient difficulty with the wording of the question, the exclusion of questions that might be related to only one type of ORL intervention, and the retention of questions that promised to provide maximum sensitivity to change.

In scoring the GBI, the responses to all 18 questions were averaged, so all questions had equal weight. The average score was then transposed onto a benefit scale ranging from −100 (maximal negative benefit), to 0 (no benefit), to +100 (maximal benefit). The statistical analysis used to compare the GBI scores for above- and below-criterion groups was a Mann-Whitney U test using a significance level of $p < .05$.

Study 1: Middle Ear Surgery Aimed at Improving Hearing. Of the 181 respondents who had surgery to improve hearing at the Glasgow Royal Infirmary, there were 68 myringoplasties, 61 stapedectomies, 29 tympanoplasties, and 23 ossiculoplasties. Surgery was performed a mean of 4 years previously (SD 3 years). The response rate was 64% (181/282). The mean age of the respondents was 53 years (SD 14 years), and 113 of the 181 patients were female.

The criterion was selected to be a measure of technical success based on pure tone thresholds, which were measured by the UK standard procedure.[15] The change in average air conduction threshold in the operated ear, calculated over 0.5, 1, 2, and 4 kHz, was derived from audiometric measures made on average 1 month before and 20 months after surgery. Hence, a four-frequency average air conduction threshold was measured preoperatively and also postoperatively. The difference between the two was regarded as the criterion, where a positive difference represented an improvement in hearing.

Figure 2 (panel 1) shows the mean GBI score for those who have experienced an improvement in average four-frequency threshold of less than 15 dB (open circles) and for those who have experienced an improvement of more than 15 dB (closed circles). The fence of 15 dB is arbitrary, and was selected to split the sample into two roughly equal groups. Moreover, an improvement in air conduction thresholds of less than 15 dB is not usually noticeable. Error bars show the 95% confidence interval on the mean. When surgery resulted in little improvement in hearing, patients reported 0 benefit, whereas those who had an improvement in hearing reported +34 benefit. The difference was significant. The study shows that when surgery results in little or no technical success, patients report little to no benefit from the intervention.

Study 2: Cochlear Implant. This was a study of 184 respondents who were provided with a cochlear implant device by one of nine UK hospitals between 1990 and 1994. The response rate was high at 86% (184/214), perhaps because these patients had previously participated in a major study on cochlear implant evaluation.[16] The mean age of the patients was 48 years (SD 16 years). Although the majority of patients received a multichannel implant (159/184), some received a single-channel implant (25/184). Listeners given a multichannel implant were provided with information on the speech amplitude, fundamental frequency, and first and second formants. Those given a single-channel implant were provided

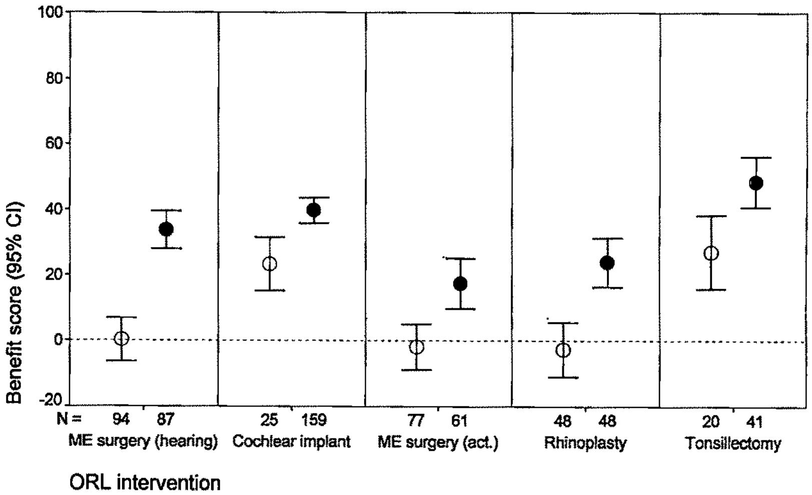

Fig 2. Mean benefit scores for five otorhinolaryngological (ORL) interventions. Parameter is criterion used to classify patient group; unfilled and filled circles represent responses from patients classified as below and above criterion, respectively. For details on criterion for each intervention, see text. Error bars — 95% confidence interval on mean, ME — middle ear, act. — activity.

with information on the speech amplitude only. As a multichannel implant provides more information than a single-channel implant and as it provides more benefit as measured by speech intelligibility measures, the criterion selected for this study was the distinction between multichannel and single-channel implants. We would expect that greater benefit would be reported by those implanted with a multichannel implant than by those implanted with a single-channel implant.

Figure 2 (panel 2) shows that both groups of implant patients showed considerable benefit as measured by the GBI. However, those fitted with a single-channel implant (open circles) reported +23 benefit, whereas those fitted with a multichannel implant (closed circles) reported +40 benefit, and this difference in benefit was significant. The criterion chosen related to the device implanted, rather than the technical success of the surgery. Hence, data for the below-criterion interventions still show considerable benefit from implantation. The ability of the GBI to discriminate between degrees of benefit related to the two types of devices indicates that it is sensitive to the changes in health status resulting from this intervention.

Study 3: Middle Ear Surgery Aimed at Eradicating Ear Activity. We studied 138 respondents who, at the Glasgow Royal Infirmary, had mastoid or middle ear surgery intended to eradicate ear activity. There were 122 cases of mastoid surgery (39 atticotomy, 23 radical, 46 modified radical, and 14 cortical) and 16 cases of myringoplasty, where the primary aim was to eradicate ear activity. Surgery was performed a mean of 6 years previously (SD 6 years). The response rate was 72% (138/192). The mean age of patients was 50 years (SD 16 years), and 78 of the 138 patients were male.

The criterion was the patient self-report of ear discharge after surgery. If patients reported no ear discharge following surgery, it was rated as above criterion, whereas the presence of ear discharge was rated as below criterion. As the presence of ear discharge is the primary complaint of the patient preoperatively, it was deemed appropriate to ask patients about ear discharge at the time of GBI completion.

Figure 2 (panel 3) shows the GBI score for those patients who reported ear discharge after surgery, and for those who reported no discharge. The data show that the GBI score discriminates between the two groups. Patients who experienced discharge following surgery reported a mean of −2 benefit, whereas patients who experienced no discharge reported +17 benefit, and this difference was significant. The criterion used in this study was related much more closely to technical success, and so those patients who were classified as below criterion reported little to no benefit from the intervention.

Because surgeons will often try to improve a patient's hearing while performing a mastoid procedure, and because a myringoplasty will improve hearing as well as reduce ear discharge, it is necessary to check that the GBI did not measure a surrogate effect related to improved hearing in the above-criterion group. Preoperative and postoperative audiometry was only available in 73 of the 138 patients. The change in average four-frequency threshold was calculated by the method previously described in study 1. The mean change in threshold for 43 patients who reported a discharging ear after surgery was −3 dB, and this compares with a threshold change of −0.1 dB for the 30 patients who reported no discharge. The difference in threshold changes between the above- and below-criterion groups is small, and so it is unlikely that hearing improvement affected the benefit score in this study.

Study 4: Rhinoplasty. This was a study of 96 respondents who had rhinoplasties performed between 1990 and 1994 at the Glasgow Royal Infirmary.[17] This group included both traumatic and nontraumatic nasal deformities. The response rate was 43% (96/224), the mean age was 36 years (SD 10 years), and 75 of the 96 patients were male.

The criterion used was the Nasal Symptom Questionnaire (NSQ), which is a self-report instrument that questions patients on nasal obstruction, postnasal drip, and reduction in the sense of smell.[18] The more symptoms reported, the lower the NSQ score. The criterion was based on the median NSQ score. The result of the comparison between GBI score for the above- and below-criterion groups may be seen in Fig 2 (panel 4). Patients who reported a high number of postoperative nasal symptoms showed an average −3 benefit, whereas those who reported a low number of nasal symptoms showed an average +24 benefit. The difference was significant. This study used a criterion that was related to the technical success of surgery. Those patients who had experienced surgery that would be regarded as less successful reported little or no benefit from the intervention.

Study 5: Tonsillectomy. In this study, the 61 respondents had tonsillectomies performed at Law Hospital in 1992-1993 (P. White et al, unpublished observations). Of these 61 patients, 9 were adults and 52 were children (less than 16 years of age). When children were unable to complete the form, we asked parents to complete the GBI on behalf of the child, and this occurred in 47 of the 52 cases. The response rate was 60% (61/102), patients had a mean age of 10 years (SD 5 years), and 32 of the 61 patients were female.

Patients were also asked whether the state of their throat had become worse, remained the same, was better, or was cured. No patients reported that their throat had become worse or remained the same, 20 of the 61 patients reported that their throat had become better, and 41 of the 61 patients reported that their throat was cured. The criterion used to test the GBI was whether the throat was better or was cured. The results are shown in Fig 2 (panel 5). Patients who reported that their throat was better reported +27 benefit, whereas patients who reported that their throat was cured reported +49 benefit, and this difference in benefit score was significant. This study shows that the GBI is sensitive to the changes in health status resulting from tonsillectomy, even when the technical outcome of the surgery is highly successful. However, these data were obtained by proxy, rather than from the patients themselves, and so the result requires confirmation from a study of adult patients.

General Discussion. The GBI was able to measure the patient benefit associated with five different ORL interventions, and discriminated between above- and below-criterion outcomes as measured by an independent measure associated with each intervention. It therefore appears to be an appropriate measure of patient benefit, with potential application to audit, research, and health policy planning. The GBI has been shown to be related to measures of technical success on the two types of middle ear surgery and on rhinoplasty. In all three studies, the below-criterion group rated themselves as having experienced little to no benefit from the intervention. These data show that the GBI is not unduly affected by the positive response bias that characterizes measures of patient satisfaction.[12,13] This was confirmed by examining the response distributions of the GBI for each of the studies. The distributions were close to normal and did not show positive skews.

The cochlear implant study used a criterion that was unrelated to technical success. A distinction was made between those who received a single-channel or a multichannel device. Given the data from the study on middle ear surgery for hearing, a criterion based on a technical success measure such as speech identification without visual cues would have improved the discriminability of the GBI. Unfortunately, these data are not available. Nevertheless, the GBI was able to discriminate between users with a single-channel device and those with a multichannel device, and this provides further evidence that the inventory is related to the amount of benefit rather than to "halo" effects associated with the surgical procedure. If the GBI were affected by "halo" effects, the distinction between the two patient groups would have been more difficult to show.

PART II: WHAT DOES THE GBI MEASURE?

The second part of the study investigated what the GBI actually measures by employing a statistical technique known as factor analysis. This technique uses the overall pattern of patient responses to identify a small number of factors that represent the underlying relationships among the 18 questions of the GBI. In other words, factor analysis enables the grouping together of the questions constituting the inventory, based on the responses given by patients. The factor structure is used to generate subscales of the GBI, which provide further information on the nature of the patient-centered outcome from different ORL interventions.

Factor Analysis. The data set was constructed to provide an overall view of patient benefit across ORL interventions. Rather than pool all the data across all studies, we randomly selected equal numbers of patients from each study. The tonsillectomy data were excluded, because a large number of the responses were completed by parents on behalf of their children. Moreover, the studies on middle ear surgery to improve hearing and on cochlear implantation were considered related, because they shared a common aim. Of the 288 cases selected, 96 cases represented an intervention aimed at the improvement of hearing (48 middle ear and 48 cochlear implant procedures), 96 cases represented surgery aimed at the eradication of ear activity, and 96 cases represented surgery aimed at improvement of nasal blockage and appearance.

A factor analysis, using principal components extraction with orthogonal rotation, was performed on the composite data set, and this yielded a three-factor solution that explained 69% of the variance. The first field under each factor in Fig 3 shows a simplification of the factor pattern matrix, where a filled square represents a loading coefficient above 0.55 for each of the 18 GBI questions. The factor loading coefficient is the correlation between the individual question and the underlying factor. Figure 3 shows that the pattern was simple, as 12 questions loaded onto factor 1, and 3 questions each on factors 2 and 3.

The simple factor loading aided interpretation, with factor 1 being identified as general benefit, factor 2 as social support, and factor 3 as physical

	Factor 1	Factor 2	Factor 3
Has the result of the operation affected the things you do?	■ ● ● ● ●		
Have the results of your operation made your overall life better or worse?	■ ● ● ● ●		
Since ..., have you felt more or less optimistic about the future?	■ ● ● ● ●		
Since ..., do you have more or less self-confidence?	■ ● ● ● ●		
Since ..., do you feel better or worse about yourself?	■ ● ● ● ●		
Since ..., have you found it easier or harder to deal with company?	■ ● ● ● ●		
Since ..., do you feel more or less confident about job opportunities?	■ ● ● ● ●		
Since ..., do you feel more or les embarrassed when with a group of people?	■ ● ● ● ●		
Since ..., do you feel more or less self-conscious?	■ ● ● ● ●		
Since ..., are you more or less inconvenienced by your (specific) problem?	■ ● ● ● ●		
Since ..., have you been able to participate in more or fewer social activities?	■ ● ● ● ●		
Since ..., have you been more or less inclined to withdraw from social situations?	■ ● ● ● ●		
Since ..., do you feel that you have more or less support from your friends?		■ ● ● ● ●	
Since ..., do you feel that you have had more or less support from your family?		■ ● ● ● ●	
Since ..., are there more or fewer people who really care about you?		■ ● ● ● ●	
Since ..., have you been to your doctor more or less often?	●		■ ● ● ●
Since ..., if there is something going around, do you usually catch it more or less often?			■ ● ● ●
As a result of your operation, have you had to take more or less medicine?			■ ● ● ● ●

Fig 3. Factor structure of GBI.

benefit. Figure 3 shows that the 12 questions that primarily loaded on factor 1 were related to general changes in health status, as well as changes in psychosocial health status. The three questions loading on factor 2 were related to the amount of social support, and the three questions loading on factor 3 were related to changes in physical health status. To ensure the robustness of the pattern matrix, an individual factor analysis was performed on each of the studies on middle ear surgery to improve hearing, cochlear implant, middle ear surgery for ear activity, and rhinoplasty. Again, the tonsillectomy study was excluded on the grounds that the patient responses were generated by proxy. The results are shown in fields 2, 3, 4, and 5 under each factor shown in Fig 3. Again, each filled circle represents a loading coefficient above 0.55. That a similar pattern matrix was generated for each of the studies shows that the factor structure was robust and replicable across studies. With two relatively minor exceptions, the responses to all questions loaded strongly and consistently across the three factors. The two exceptions were related to the third factor. First, the responses to the question regarding visits to the doctor from patients who had middle ear surgery to eradicate ear activity loaded primarily onto factor 1 rather than factor 3. Second, the loading coefficient for rhinoplasty responses to the question regarding viral infections was comparatively low at 0.43.

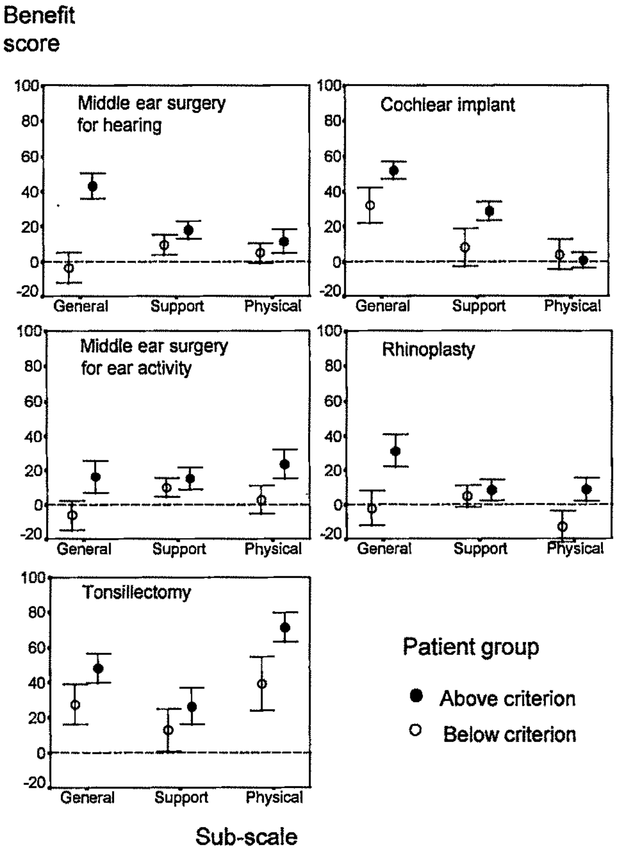

Fig 4. Profile scores for five ORL interventions. Category axis represents benefit score associated with each of three subscales of GBI. General — general benefit, Support — social support, Physical — physical benefit. Other details as for Fig 2.

Profile Scores for GBI. Subscales of the GBI were formulated that consisted of questions that loaded highly on a given factor. The provision of subscales yields a profile as well as an overall benefit score, and provides further information on the nature of patient benefit associated with each ORL intervention. Scoring of the subscales was similar to that undertaken to obtain the overall score; the average response to each question associated with each factor was calculated. Hence, it was assumed that the factor loading was unity when factor coefficients had reached a criterion of 0.55, and zero when the coefficient was below 0.55. This is a simplification of a factor-weighted score, and the decision was made on the grounds of improved clinical application. To provide a comparison with the overall score, the average score for each subscale was transposed on a benefit scale ranging from −100 to +100.

The results of the profile scoring method are shown in Fig 4 for each of the ORL interventions. The subpanels in Fig 4 show how the profile changed according to the relative success of each ORL intervention, and show that the profile pattern varied according to the intervention. Error bars represent the 95% confidence interval on the mean.

Figure 4 shows profile scores associated with middle ear surgery to improve hearing, in which the parameter is the change in air conduction threshold. The general and support subscales show a significant difference between patients who were above and below criterion, but showed no significant difference for the physical subscale. A similar pattern is shown in Fig 4 for the data for cochlear implant patients. These data show that patients reported high rates of benefit for both single-channel and multichannel devices. However, those implanted with multichannel devices reported significantly more changes in their general health status and social support than those implanted with single-channel devices. There was no difference in reported changes of physical health status.

Subscale responses for middle ear surgery for ear activity, for rhinoplasty, and for tonsillectomy are reported in Fig 4. Like the two previous interventions, these all showed significant changes in general benefit. There were, however, two marked contrasts with the two interventions with a primary aim to improve hearing. First, there was no significant difference in social support between above- and below-criterion patient groups. Second, the above-criterion patients reported a significant improvement in their physical health status, compared with those who were classified as below criterion.

The different profile responses associated with each ORL intervention showed that each subscale contributed to different aspects of patient benefit. Interventions aimed at improving hearing resulted in improved social support, whereas interventions aimed at eradicating ear activity, reducing nasal symptoms, or alleviating sore throat resulted in a change in physical health status. Therefore, the GBI provides an overall score, which is useful to compare results across interventions, as well as a profile score, which provides additional information on the nature of patient benefit associated with an ORL intervention.

CONCLUSIONS

The GBI is a patient-oriented measure of benefit, and has been shown in the first part of this paper to measure the change in health status resulting from five different ORL interventions. The GBI discriminated between groups independently classified as above or below criterion in each intervention. The second part of the paper showed that the factor structure of the GBI was robust, and demonstrated the use of subscales associated with the factor structure.

It is likely that the GBI is applicable to other surgical interventions, given its high sensitivity to each of the five ORL interventions. Moreover, the GBI is probably applicable to nonsurgical ORL interventions, because the benefit from cochlear implantation derives primarily from the device, rather than the surgery. If the surgery were providing the major benefit in cochlear implant, then no differences in patient benefit between the single-channel and multichannel devices should have been found. As the GBI was responsive to cochlear implantation, it should also be responsive to other device-based interventions such as the provision of hearing aids.

There are at least three limitations to the present study. First, the validity of the inventory should be further established by comparing its responsiveness with that of a well-known measure such as the Short Form-36.[9,10] Second, as mentioned previously, the research reported here is retrospective and therefore limited to the experience of patients who had surgery some years before. Patient's memories of surgery and its effects will fade with time, and this will affect the reported outcome. However, in a separate analysis of this study, the number of years since surgery was not found to affect the overall score. The shortcomings of a retrospective approach are recognized. Prospective studies of patients undergoing surgical procedures to improve hearing and to eradicate ear activity, as well as of patients who have been provided hearing aids, are currently in progress.

The third limitation of the GBI is that it was configured to be maximally sensitive to the change in health status that occurs following intervention. The GBI is a measure of patient benefit, and not of health status per se. It measures the changes in health status resulting from ORL intervention, but does not provide a measure of the status of the patient either prior to or after the intervention. We are currently working on a health state version of the GBI, and expect to compare both the benefit and health state versions of the GBI with existing measures such as the SF-36.

In summary, we have shown that the GBI was applicable to a number of different ORL interventions, and has a high sensitivity to change. Although further research is appropriate, it would appear to be relevant to a number of potential applications, including audit, retrospective and prospective studies, health policy, and resource allocation.

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QUALITY OF LIFE AFTER ACOUSTIC NEUROMA SURGERY

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A questionnaire was sent to 134 patients who had undergone surgery for a unilateral acoustic neuroma between 1980 and 1993, to obtain data on the consequences on their quality of life, physical condition, social life, employment, and use of medical facilities. Distinctions were made between the translabyrinthine-transotic approach, the suboccipital approach, the tumor size, and the number of operations per patient. We found that the patients' reported state of health after surgery was poorer than that in a group of comparable nonoperated patients. Recuperation after an operation took many months and did not always result in full recovery. Surgery had various effects on preoperative symptoms such as hearing loss, tinnitus, vertigo, and facial nerve dysfunction: improvement, no change, or deterioration. Surgery had severe consequences on social life and occupation, but far less effect on income. Almost one third of the patients required postoperative home help, and a proportion were declared unfit to work. The surgical approach, tumor size, and reoperations had a definite influence on the study parameters. After suboccipital surgery, there were more reports of pain, more declarations of incapacity to work, poorer facial nerve function, and more frequent visits to the general practitioner. The translabyrinthine-transotic approach was associated with more severe pain and more complaints of postoperative vertigo. A greater proportion of the patients with larger tumors were declared unfit to work. The general state of health after suboccipital reoperations was better than after the initial operation; there was no reasonable explanation for this. Facial nerve function deteriorated after reoperation(s).

KEY WORDS — acoustic neuroma, quality of life, suboccipital approach, translabyrinthine approach, tumor size.

INTRODUCTION

A patient's subjective assessment of the outcome of therapy is an important measure of therapeutic success. Whereas many reports have been published in the literature on the results of acoustic neuroma surgery after various approaches to various tumor diameters, the subjective opinion of the patient about the postoperative period has received far less attention. Parving et al[1] and Wiegand and Fickel[2] mentioned a decrease in the quality of life after acoustic neuroma surgery. Surgical intervention can strongly influence the daily life of the patient. The consequences of the intervention on tumors of the same diameter can vary depending on the choice of surgical approach. So far, no research has been conducted in which a comparison was made between the effects of tumor size, various approaches, and reoperations. At the University Hospital Nijmegen, patients with an acoustic neuroma can be operated on via the suboccipital approach or via the translabyrinthine-transotic approach. Although the suboccipital approach is used for the majority of large tumors and the translabyrinthine-transotic approach for the majority of small tumors, the overlap in tumor size means that a fairly reliable comparison can be made. Many different effects of tumor size, approach, and reoperations can be expected. Larger tumors may have more postoperative consequences on the quality of life than smaller ones. Surgical results have shown remarkable differences in facial nerve function in relation to the number of reoperations.[3,4] Reoperations after subtotal removal may lead to greater morbidity. The results of our quality of life measurement were also compared to those of a group of nonoperated Dutch inhabitants. The outcome of the study may be used for patient education, to assist in the choice of approach, and to encourage further research.

PATIENTS AND METHODS

In the period from 1980 to the end of 1993, 176 patients were operated on for a unilateral acoustic neuroma at the University Hospital Nijmegen. The suboccipital approach was used in 108 patients, and the translabyrinthine or (modified) transotic approach in 66 patients. Two patients were operated on via the middle fossa approach and were excluded from the study.

In May 1994, the remaining 174 patients were sent a questionnaire with an instruction sheet about how to fill it in. The questionnaire comprised three sections: the consequences of the operation on 1) quality of life, 2) physical condition, and 3) the use of medical facilities. The results are discussed per section.

Quality of life was measured by means of generic and disease-specific measurement instruments and a number of questions about changes in relation to home help requirement, work (resuming work, being declared unfit to work), and income. The generic and

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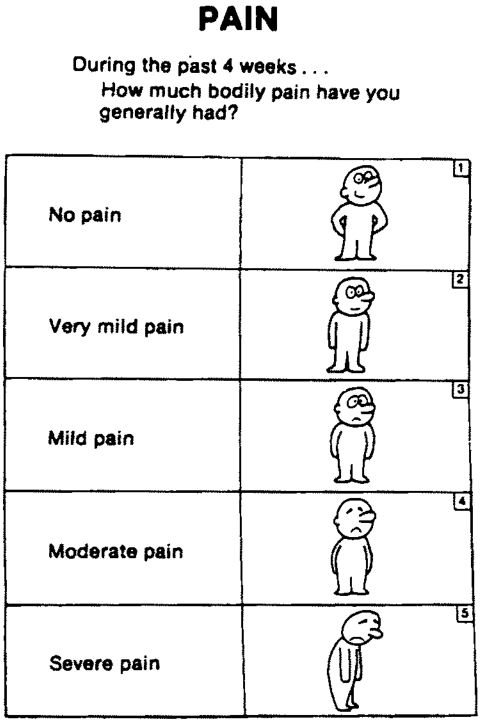

PAIN

During the past 4 weeks . . .
How much bodily pain have you generally had?

No pain		1
Very mild pain		2
Mild pain		3
Moderate pain		4
Severe pain		5

Fig 1. Example of COOP/WONCA pain chart.

disease-specific measures for quality of life are described briefly below.

The standard question of the CBS (Dutch Central Bureau of Statistics) was used to measure the state of health: "What is your general state of health?" We inquired about the patient's state of health at that time. Answers could be given on a 5-point scale (1 = very good, 5 = poor). The answers were compared to those obtained in 1991 and 1992 from a Dutch population of the same age.[5] The COOP/WONCA[6] (Dartmouth COOP Functional Status Assessment Charts ["COOP charts"] from the World Organisation of Family Physicians/General Practitioners [WONCA]) was also used as a generic measure of quality of life. This instrument converts issues such as physical fitness, feelings, daily activities, social activities, pain, change in health, and general health. The state of health for these issues could be marked on a 5-point scale (one for each question). Figure 1 shows the COOP/WONCA pain chart. A total of 7 questions were used to gain an impression of the functional status of each patient over the preceding 2-week period. This was defined as the ability of a person to perform in and adapt to his or her environment.

The Cancer Rehabilitation Evaluation System–Short Form (CARES-SF)[7] (Dutch translation) was used to develop our own disease-specific measurement instrument. The adapted version comprised 3 scales and a number of separate items; specific questions about breast cancer, prostate cancer, or intestinal cancer were omitted. The scales inquired about physical condition (8 items), psychosocial condition (13 questions), and several relational aspects. There were separate items about the adequacy of the information provided by the doctors, financial problems, insurance problems, and transportation difficulties. A total of 30 items were presented on the questionnaire. The question asked whether a specific problem had been applicable to the respondent during the preceding 4-week period. Answers could be given on a 5-point scale (0 = not at all, 4 = very much).

The physical condition of the patient as a result of cerebellopontine angle surgery was determined on the basis of the surgical effects on hearing (as experienced by the patient with both ears), tinnitus, vertigo, and facial nerve function. Hearing was measured by asking whether it had been adequate (good) or inadequate (poor) preoperatively and whether it had improved, remained the same, or deteriorated after the operation. Facial nerve function was measured as a percentage. There were 6 categories from 0% to and including 100%, in steps of 20%. This 6-step scale was in some degree similar to the House-Brackmann scale with 6 grades[8]; 100% and 0% were equivalent to House grades I and VI, respectively. The patients were also asked whether they had been using a hearing aid, or had ever received treatment to improve facial nerve function; in addition, they were asked to give their own opinion of whether recovery was complete (100%) or partial (at least 50%) and how long this had taken.

Use of medical facilities were measured by means of questions from the CBS about the number of visits to a general practitioner (GP), specialist, physiotherapist, or homeopathist and number of admissions to a hospital. The outcomes were compared to average values for the use of medical facilities in the Netherlands.

On each questionnaire that was returned to us, the treating physician recorded the operation date, surgical approach, tumor size, number of reoperations, and postoperative facial nerve function (if possible 1 year after the operation).

The questionnaires were analyzed anonymously. Not all the patients had answered all the questions. In the results we mention how many had answered a particular item. The outcomes were indexed to patient data such as age and sex.

Two surgical approaches were distinguished: translabyrinthine-transotic and suboccipital. Tumor size was defined as the maximum diameter, including the intrameatal part. Contrast was made between small tumors (≤ 25 mm) and larger tumors.

TABLE 1. APPROACH, TUMOR SIZE, AND REOPERATIONS IN 134 PATIENTS

	Translabyrinthine-Transotic Approach		*Suboccipital Approach*	
No. of Patients	*Tumor ≤25 mm*	*Tumor >25 mm*	*Tumor ≤25 mm*	*Tumor >25 mm*
With one operation	51/134 (38%)	2/134 (1%)	21/134 (16%)	43/134 (32%)
With more than one operation	1/134 (1%)	1/134 (1%)	1/134 (1%)	14/134 (10%)
Total	52/134 (39%)	3/134 (2%)	22/134 (16%)	57/134 (43%)

The EPI-INFO computer program was used for data input. Statistical analyses were performed with SPSS/PC+ (Statistic Program for the Social Sciences/Personal Computer version), the χ^2 test, and an analysis of variance. As the maximum follow-up period of the patients was 14 years, the operation date was incorporated as a covariable.[9] In this way, the effects were corrected for the length of the postoperative period, and we also compensated as much as possible for whether the operation had taken place many years ago or recently.

An important condition for such an analysis is to ensure that the so-called parallel assumption is not violated. We fulfilled this condition. The results are presented in a simple manner: the corrected means are given without mentioning any data related to the parallel assumption and the size of the covariable. P values are given for significant differences. In the analyses, the effects of the surgical approach and tumor size were evaluated especially. Distinction was made between patients who had undergone one operation and those who had undergone one or more reoperations.

RESULTS

The questionnaire was sent to 174 patients. A total of 40 questionnaires could not be used in the analyses because the patient had moved and was untraceable (n = 14), or the patient had refused to participate (n = 17) or had died (n = 9). The response rate in the total group was 89% (134/151): 88% (79/90) in the suboccipital approach group and 90% (55/61) in the translabyrinthine-transotic approach group. The study population comprised 68 men and 66 women, with an average age of 53.95 years (SD = 14.45) at the time the survey was conducted. The difference in age between the men and women was not significant. There was no significant difference between the sexes, ages, or approaches in relation to a certain tumor size and whether or not reoperations had been necessary. Table 1 shows the distribution of the patients according to the approach and tumor size.

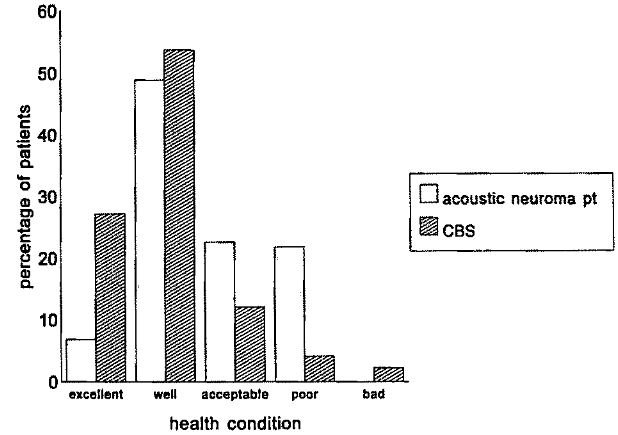

Fig 2. General state of health of patients after surgery for unilateral acoustic neuroma compared to data from Dutch Central Bureau of Statistics (CBS).

Patients with a translabyrinthine-transotic approach and a tumor diameter of larger than 25 mm were excluded from the analyses incorporating approach and tumor size because of low numbers (n = 3). In 17 patients, reoperation had been necessary owing to recurrence after subtotal or near-total removal. These operations were mainly conducted after a suboccipital approach with a tumor diameter of larger than 25 mm. The reason for this was the large number of subtotal suboccipital operations performed at our clinic.[4] Analyses on the effect of whether or not reoperations had been necessary were only performed on the group with a suboccipital approach and a large tumor because of the low number of patients with reoperations in the other groups. Table 1 also shows how many patients underwent reoperations per approach and tumor size.

General State of Health. In answer to the CBS question on the general state of health, the patients with reoperations (mean = 2.27) reported better health than those who had only undergone one operation (mean = 2.82, F(1,54) = 4.54, p < .04). It was not possible to explain this unexpected effect. There was no significant difference between the surgical approaches. All the data on the patients with acoustic neuroma surgery were compared to the CBS data for the general Dutch population: the state of health of the patients was considerably poorer than that of the general population (Fig 2). The answers given by the patients with and without reoperations for 3 of the 7 COOP/WONCA questions (pain, general health, and feelings) were significantly different. Patients with reoperations (mean = 1.80) reported significantly less severe pain than the patients without reoperations (mean = 2.75, F(1,50) = 5.07, p < .03). Patients with reoperations (mean = 2.05) reported better general health than the patients without reoperations (mean = 1.57, F(1,50) = 3.24, p < .08). It would be obvious to

TABLE 2. OVERALL PREOPERATIVE AND POSTOPERATIVE HEARING IN 128 PATIENTS

Overall Hearing After Surgery	*Poor Preoperative Hearing (N = 119)*	*Good Preoperative Hearing (N = 9)*
Improved	1/119 (1%)	0/9 (0%)
Unchanged	70/119 (59%)	8/9 (89%)
Deteriorated	48/119 (40%)	1/9 (11%)

Overall hearing according to patients' view (two ears).

ascribe this unexpected effect to the difference in the level of pain experienced by the patients with and without reoperations. As the level of pain decreased, the state of general health increased. The COOP/WONCA answers showed that the patients with a suboccipital approach, irrespective of the diameter of the tumor (mean = 2.3 small tumor; mean = 2.37 larger tumor), had more emotional problems than the patients with a translabyrinthine-transotic approach (mean = 1.80, $F(2,98) = 2.37$, $p < .10$). The disease-specific measure for the quality of life (the CARES-SF) comprised three scales. These scales were found to be reliable in this study. Crohnbach's α was 0.83 for the physical scale, 0.81 for the psychosocial scale, and 0.75 for the relational scale. The answers to the CARES-SF showed very little difference between patients with and without reoperations or between the surgical approaches and tumor diameters. Only the psychosocial scale revealed a difference between patients with and without reoperations ($F(13,40) = 1.95$, $p < .06$). The difference was mainly based on two items: "finding it difficult to sleep" ($F(2,52) = 5.09$, $p < .03$) and "worrying about becoming dependent on others in the future" ($F(2,52) = 4.48$, $p < .01$). When the patients with reoperations were compared to those without reoperations, the former had less difficulty with sleeping (mean = 1.15 versus mean = 0.35), but were more worried about the time that they would no longer be able to look after themselves (mean = 0.99 versus mean = 1.76). On an item level, one more effect could be seen. Irrespective of the tumor diameter (mean = 0.74 small tumor; mean = 0.72 larger tumor), more of the patients with a suboccipital approach complained of pain than the patients with a translabyrinthine-transotic approach (mean = 0.37, $F(2,111) = 2.46$, $p < .10$). It was concluded that there was more frequent pain after a suboccipital approach (CARES-SF), but that it was less severe (COOP/WONCA) than after a translabyrinthine-transotic approach. The CARES-SF items could be expressed as one collective quality of life measure. This measure comprised the sum of all the answers given. No significant differences were found between the patients with and without reoperations or between the two approaches for a certain tumor diameter. The quality of life of the patients was influenced to a limited extent (some questions on the CARES-SF) by the surgical approach and whether or not reoperation(s) had been necessary.

A high level of satisfaction (93%) was expressed about the preoperative information and counseling provided by the doctors and nurses.

Influence of Operation(s) on Home Help. A total of 41 of 130 patients (32%) required home help after the operation(s); 36 only required help with housekeeping tasks. Two patients also needed medical care and help with their personal care. All three forms of help were required by 1 patient. The help was provided for payment by third parties (45%), by members of the family (44%), or by a combination of the two, sometimes with other relatives or neighbors (11%). Receiving help was not related to the age of the patient.

Employment. A distinction was made between paid work and unpaid work. We asked about the situations 3 months before the operation and 1 year afterward. Preoperatively, 59 of 134 patients (44%) had paid employment; 75 of 134 patients (56%) had unpaid work. One year after the operation, 49 of 134 patients (37%) had paid work and 85 of 134 (63%) had unpaid work. At 1 year postoperation, paid or unpaid work had been resumed fully by 54% and partly by 15%; 31% were no longer able to work (n = 94). About 10% of the patients had found alternative employment (n = 94). In the Netherlands, it is possible for long-term patients to be given leave of absence from work during the evaluation period while retaining partial pay. Of the 119 patients who answered this question, 31 patients (26%) were declared unfit to work according to these norms. The number of patients with a large tumor in this group was significantly higher than the number with a small tumor ($\chi^2 = 9.15$, $p < .005$). Suboccipital surgery led significantly more often to being declared unfit to work than translabyrinthine-transotic surgery ($\chi^2 = 5.96$, $p < .05$). The main reasons were vertigo and hearing impairment.

Income. Only 67 of 134 patients (50%) provided information about their income. The income of 24 of 67 patients changed, and in 21 of 67 it decreased, as a result of the operations. Two patients who were self-employed encountered financial problems after the operation.

Physical Health in Relation to Hearing, Tinnitus, Vertigo, and Facial Nerve Function. The surgical approach, tumor size, and reoperations did not have

TABLE 3. PREOPERATIVE AND POSTOPERATIVE COMPLAINTS OF TINNITUS IN 106 PATIENTS

Tinnitus After Surgery	*Preoperative Tinnitus (N = 81)*	*No Preoperative Tinnitus (N = 25)*
Improved	20/81 (25%)	1/25 (4%)
Unchanged	32/81 (40%)	18/25 (72%)
Deteriorated	29/81 (36%)	6/25 (24%)

TABLE 4. PREOPERATIVE VERSUS POSTOPERATIVE RESULTS OF 23 PATIENTS WITHOUT VERTIGO

	Translabyrinthine-Transotic Tumor	*Suboccipital Tumor*	
Postoperative Vertigo	*≤25 mm (N = 10)*	*≤25 mm (N = 5)*	*>25 mm (N = 8)*
Absent	4/10 (40%)	4/5 (80%)	5/8 (63%)
Present	6/10 (60%)	1/5 (20%)	3/8 (38%)

any influence on hearing (Table 2) and tinnitus (Table 3); in the further analyses we did not distinguish between them. A remarkably large proportion of the patients without vertigo preoperatively (Table 4, $n = 23$) had vertigo complaints after translabyrinthine-transotic surgery. Some of the patients with vertigo before the operation (Table 5, $n = 63$) mentioned improvement after suboccipital surgery. Only 5 of 128 patients (4%) needed a hearing aid, while 99 of 128 patients (77%) had not needed a hearing aid before the operation or afterward.

Facial Nerve Function. We asked about the level of facial nerve function (patient's and treating physician's opinion), whether there were facial nerve problems before surgery, and whether adjuvant treatment was necessary after the operation. The patient's opinions about prospective facial nerve function (Table 6) were influenced significantly by reoperations ($F(1,44) = 3.11$, $p < .09$), but not by the surgical approach or the tumor size. Patients with reoperations (mean = 3.91) reported considerably poorer facial nerve function than the patients with only one operation (mean = 2.80). When the same evaluation was made by the treating physician, it was found to be influenced significantly by the surgical approach and tumor size ($F(2,111) = 3.70$, $p < .03$), but not by whether or not the patient had undergone reoperations. The most favorable facial nerve function was mentioned after a translabyrinthine-transotic approach for a small tumor, and the poorest function after suboccipital surgery for a larger tumor (mean = 2.38). Intermediate results were reported after suboccipital surgery for a small tumor (mean = 1.87). Figure 3 shows facial nerve function in House-Brackmann grades (1 year postoperatively, $n = 123$) against the percentages given by the patients (describing their present condition). The difference in evaluations between the physicians and the patients deviated in accordance with the correlation measure. There was only slight correlation between them: $r = .67$, $p < .001$. Particularly answers of 0% and 100% (the extremes) were responsible for the difference: 56.7% had 100% function according to the physician versus 44.3% according to the patients; 5.2% had 0% function according to the physician versus 12.2% according to the patients. There was reasonable agreement on the other scales.

Recovery. We inquired about the level of recovery and the time that had elapsed. Partial recovery was mentioned by 92 of 97 patients within 1 year of the operation (at least 50% recovery); 56 of 97 had recovered fully in this time. Full recovery had taken longer than 1 year in 10 of 97 patients, while 31 of 97 patients had not yet recovered fully. Surgical approach for a particular tumor size and whether or not there had been reoperations did not have any significant effects on recovery (Fig 4). Adjuvant treatment was necessary in 45 of 134 patients (34%). It mainly comprised physiotherapy (60%), plastic surgery (7%), surgical reconstruction of the facial nerve (4%), or a combination of the three (20%).

Use of Medical Facilities. The use of medical facilities was higher in the patients with acoustic neuroma surgery than in the general Dutch population. During the previous year (May 1993 to May 1994), 85.3% of the patients had visited their GP, versus 75.5% of the general Dutch population in 1991 and 1992 (of comparable age). These percentages for specialist consultations were 82.6% and 39.8%, respectively; for admissions to hospital, 20.7% and 6.9%, respectively. Rates for physiotherapy and homeopathy reported by the patients were twice as high and one and a half times as high as those of the general Dutch population, respectively. No significant differences were found in the patient group for surgical approach for a particular tumor size or whether or not

TABLE 5. PREOPERATIVE VERSUS POSTOPERATIVE VERTIGO IN 63 PATIENTS

	Translabyrinthine-Transotic Tumor	*Suboccipital Tumor*	
Postoperative Vertigo	*≤25 mm (N = 21)*	*≤25 mm (N = 10)*	*>25 mm (N = 32)*
Improved, fewer complaints	6/21 (29%)	3/10 (30%)	15/32 (47%)
Unchanged or deteriorated, more complaints	15/21 (71%)	7/10 (70%)	17/32 (53%)

TABLE 6. PATIENT'S VIEW OF FACIAL NERVE FUNCTION IN 126 CASES

	Preoperative (Some) Facial Paresis (N = 21)			*Preoperative Normal Facial Nerve Function (N = 105)*		
	Translabyrinthine-Transotic Tumor	*Suboccipital Tumor*		*Translabyrinthine-Transotic Tumor*	*Suboccipital Tumor*	
	≤25 mm (N = 4)	*≤25 mm (N = 4)*	*>25 mm (N = 13)*	*≤25 mm (N = 48)*	*≤25 mm (N = 17)*	*>25 mm (N = 40)*
Postoperative (some) facial paresis	0	0	5 (1)	13	6 (1)	21 (8)
Postoperative normal facial nerve function	4	4	8 (2)	35 (1)	11	19 (3)

In parentheses are numbers of patients with reoperations.

there had been reoperations. There was a difference in the number of times the GP had been consulted in the previous 2 months. Irrespective of the tumor size, the GP had been visited significantly more often (F(2,111) = 4.79, p < .02) after a suboccipital approach (mean = 1.11 small tumor; mean = 1.24 larger tumor) than after a translabyrinthine-transotic approach (mean = 0.47).

DISCUSSION

Very little research has been performed on the quality of life of patients after surgery on the cerebellopontine angle for the treatment of an acoustic neuroma. The best-known study was published by the Acoustic Neuroma Association[2] after the members of this patient association had been sent a questionnaire. The study group comprised patients who had encountered different treating physicians and had been operated on via various approaches at diverse centers. The study by Parving et al[1] from Copenhagen was conducted exclusively on patients who had undergone translabyrinthine surgery; the tumor size and reoperations were not included in the analyses. Aspects such as the postoperative hearing level were described, although generally only the changes in hearing in the operated ear received consideration. In this study we evaluated the effects that the surgical approach, tumor size, and reoperations had had on the quality of life and on the views of the patients.

The quality of life was closely correlated with the general state of health. After cerebellopontine angle surgery, the state of health was poorer than that in comparable groups of patients, as was shown by both the generic and disease-specific measurement instruments. It was remarkable that the state of health of the patients with reoperations was better than expected. These patients reported less pain and slept better than average. Concerns about the future, on the contrary, increased if the patient had undergone reoperations. The surgical approach had an influence on pain; the translabyrinthine-transotic approach was associated with less frequent pain, but it was more severe than the pain after suboccipital surgery. We could not find a reasonable explanation for this. After discharge from the hospital, the operation affected the situation at home; one third of the patients required home help. The operation had less effect on a patient's income, but over 25% of the patients were declared unfit to work. These mainly were patients who had under-

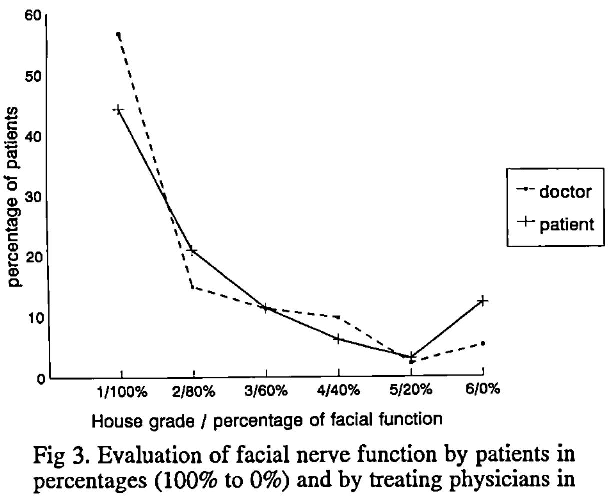

Fig 3. Evaluation of facial nerve function by patients in percentages (100% to 0%) and by treating physicians in House grades I through VI.

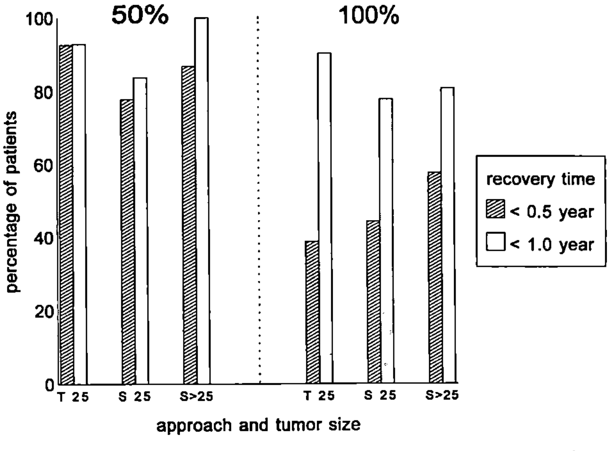

Fig 4. Duration and level of recovery per approach and tumor size; partial recovery (at least 50%) and full recovery (100%) with percentage of patients.

gone suboccipital surgery for a larger tumor.

Recovery after the operation was a long-term process, and full recovery was not always achieved. The long recovery period and problems with resuming work were also mentioned in the report on members of the Acoustic Neuroma Association.[2]

Our questions about hearing concerned bilateral hearing, with a good ear and a poor or deaf ear. According to the majority of patients, hearing (Table 3) was already poor before the operation (92%). This did not improve in the postoperative period, or it deteriorated further. Even adequate hearing was seldom spared by surgery. It was not always necessary or worthwhile to use a hearing aid for postoperative hearing impairment if only one ear was affected.

Preoperative tinnitus complaints did not often improve after surgery (25%), but they could develop (24%) or remain unchanged (40%). This is contrary to the findings of Berliner et al,[10] who reported that surgery more often improved the complaints (37%) than caused them to deteriorate (15%) and that postoperative tinnitus developed in 34%.

Before the operation, 63 of 86 of our patients had vertigo. Surgery had various effects. With small tumors, the complaints sometimes improved, but they more often deteriorated. With large tumors (suboccipital approach) the complaints generally improved postoperatively. This may have been due to a reduction in cerebral pressure after the tumor was removed. It was remarkable that some of the patients who did not have vertigo preoperatively developed complaints after translabyrinthine-transotic surgery (Table 4). This might have been caused by the removal of an as-yet-unaffected labyrinth during the operation. However, the numbers were very small.

According to the treating physician, postoperative facial nerve function was poorer after surgery for large tumors and after reoperations. The answers the patients gave on the questionnaires showed that this was not significant. This is remarkable, because the classifications of the patients and physicians were in reasonable agreement, except at the extremes (Fig 3). The latter were responsible for the final outcome of poor correlation. It is possible that paresis symptoms of the trigeminal nerve also played a role, because patients often attribute the sensitivity of the face to facial nerve function.

The patients made considerable use of medical facilities. The GP and specialist were visited more often, as were the physiotherapist and homeopathist. There were more admissions to hospitals in this patient group. The larger number of visits to the GP by patients after suboccipital surgery may have been the result of poor facial nerve function and the associated eye problems.

CONCLUSION

Cerebellopontine angle surgery had a great deal of influence on the quality of life of the patients. The postoperative recovery period was long, and recovery was not always full. Patients had a poorer general state of health and made more frequent use of medical facilities. A large proportion of the patients reported problems with their social life and work, but seldom with their income. Preoperative symptoms such as hearing loss, vertigo, and tinnitus were influenced by the operation. Facial nerve function often deteriorated postoperatively, and sometimes reconstructive surgery was necessary.

The surgical approach affected the postoperative quality of life. Facial nerve function was better in the patients with translabyrinthine-transotic surgery. This approach led to less frequent pain, but when present, pain was more severe. Fewer patients were declared unfit to work, and there were fewer visits to the GP than after suboccipital surgery. Reoperations after subtotal removal using the suboccipital approach had less influence than expected. The general state of health had even improved in some cases, but there were more emotional problems and concerns about the future. Facial nerve function deteriorated after reoperations. Larger tumors were more often associated with being declared unfit to work and reoperations than small tumors.

Adequate patient education should be based on surgical results and also consider patients' postoperative experience and opinions. For small tumors, the translabyrinthine-transotic approach seems to be preferable to the suboccipital approach. Despite good surgical results and a decreasing number of complications, there is still considerable morbidity and prolonged recovery. It is important to realize this and to prepare new patients for these eventualities.

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FOURTH INTERNATIONAL SYMPOSIUM ON CHILDHOOD DEAFNESS

The Fourth International Symposium on Childhood Deafness: Serving All Children With Hearing Loss will be held on Kiawah Island, South Carolina, October 9-13, 1996. For more information, contact Shelia Lewis, Bill Wilkerson Center, 1114 19th Avenue South, Nashville, TN 37212; telephone (615) 340-8292.

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DENTACT FOR EVALUATING MANDIBULAR AND MAXILLARY INVASION IN CANCER OF THE ORAL CAVITY

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We used a retrospective analysis of charts, imaging studies, and histologic findings when available in 17 patients with cancer of the oral cavity to define the value of DentaCT or multiplanar reformation software in assessing bony involvement by malignant tumors of the oral cavity. From two academic tertiary-referral medical centers, the 17 patients had a mean age of 63 years and suspected maxillary (2) or mandibular (15) invasion. All patients had conventional computed tomography scanning and multiplanar reformation scans with several additional imaging studies obtained. Two patients demonstrated no bony involvement by imaging and histologic studies. Twelve of the remaining 15 patients had surgically documented bony involvement also correctly detected by DentaCT. DentaCT was found to be a valuable tool in defining extent of bony invasion by tumor. Although not compared to other imaging modalities, our experience supports the use of DentaCT where available for this purpose.

KEY WORDS — cancer, computed tomography, DentaCT, mandible, maxilla, multiplanar reformation software, oral cavity.

INTRODUCTION

Methods of imaging of the mandible and maxilla include plain radiographs, panoramic radiography (panorex), bone scanning,[1,2] periapical films, three-dimensional computed tomography (CT) scans,[3,4] conventional CT scans,[5] and magnetic resonance imaging (MRI).[6,7] In assessing bony invasion by tumor, the former five techniques may be a useful adjunct to diagnosis in selected cases, but CT and MRI today play the key role in the effort to determine the full extent of tumor invasion.

Computed tomography scanning has been recommended as the primary diagnostic modality, but studies that endorse its use were either performed before MRI became generally available[5] or retrospectively cover such time periods.[8] Belkin et al[7] compared MRI with CT for evaluation of maxillary and mandibular tumors, of which 9 of 16 were malignant. Lesion detection, tumor margins, soft tissue extent, and bony involvement were separately evaluated, and MRI was found to be superior in all four categories. Patient intolerance secondary to claustrophobia, limited access, higher costs, and inability to image patients with pacemakers or ferromagnetic surgical clips may limit the usefulness of MRI. Yet, proponents of MRI stress its ability to obtain images in any plane without the need to reposition the patient, its lack of radiation, its good tumor–soft tissue interface, and its relative absence of artifacts as compared with conventional CT.[6] Clear delineation of bone marrow and cortex, high soft tissue spatial resolution, and good evaluation of lesion margins further support application of MRI.[7]

DentaScan or multiplanar reformation (MPR) software has been recently introduced for assessment of tumor invasion into the maxilla or mandible,[4,9] with good results. We have studied 17 patients with suspected maxillary or mandibular involvement with malignancy, utilizing DentaCT, an MPR program, to evaluate its efficacy in determining bony invasion by tumor.

PATIENTS AND METHOD

All scans were performed on an Elscint Elite 2400 scanner (Elscint Ltd, Haifa, Israel) with a 2.0-second scan time, 120-kV peak voltage, and 300 mA/s. The patients were placed with the examined anatomic structure parallel to the scan plane. Axial sections were acquired by use of a bone algorithm in dynamic mode, with a 512 × 512 matrix and a slice thickness of 1.2 mm. Slice increments of 1.0 mm were obtained in the mandible and maxilla. The ratio of 1:1 was used

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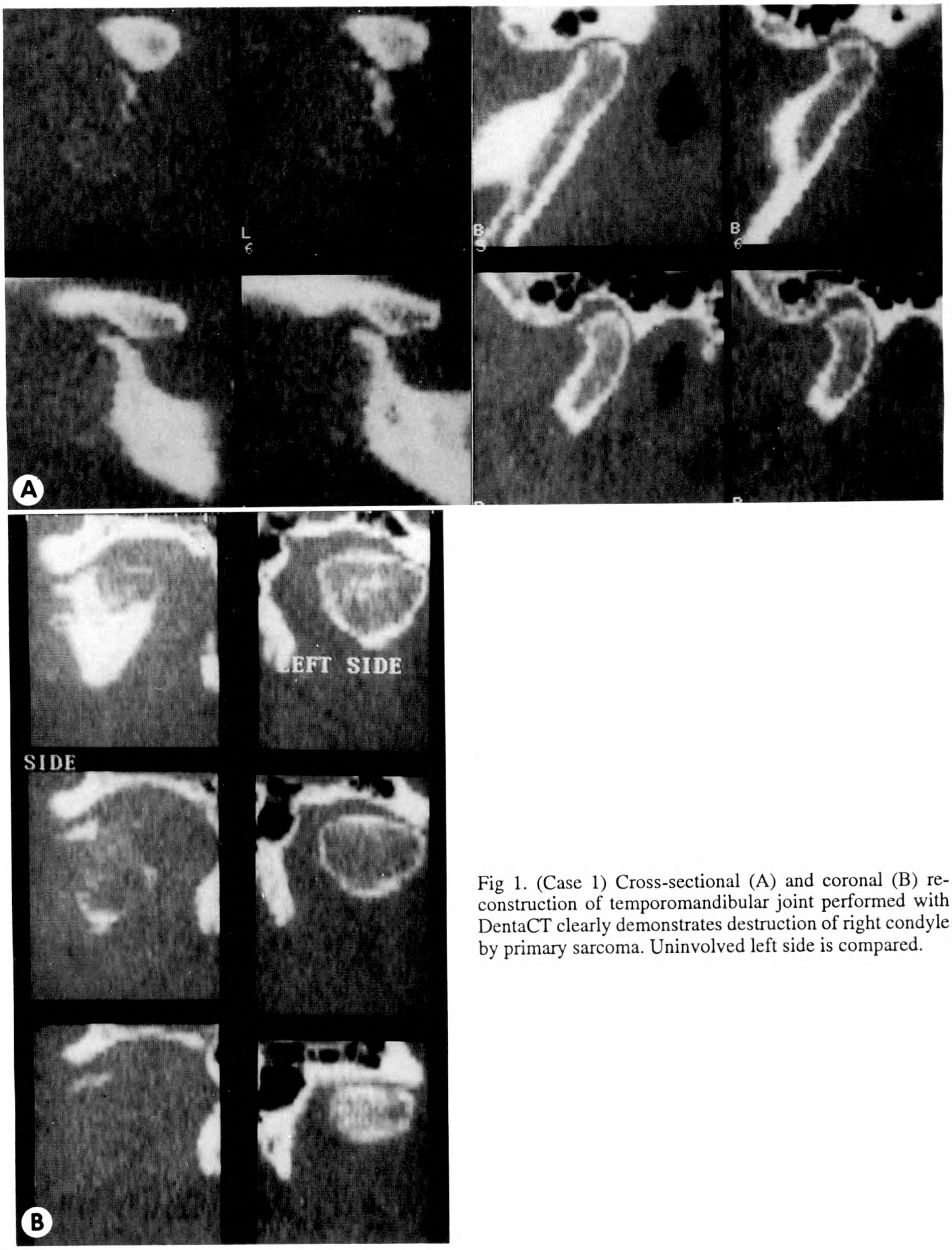

Fig 1. (Case 1) Cross-sectional (A) and coronal (B) reconstruction of temporomandibular joint performed with DentaCT clearly demonstrates destruction of right condyle by primary sarcoma. Uninvolved left side is compared.

to facilitate exact measurement.

DentaCT was used in 14 nonconsecutive cases of newly diagnosed tumors and 3 cases of recurrent tumors. Eight of the patients were women and 9 were men. Patient age ranged from 42 to 79 years with a mean of 63 years. All had obvious or suspected maxillary (2) or mandibular (15) compromise by tumor. There were 11 squamous cell cancers (SCCs), 1 osteosarcoma, 1 chondrosarcoma, 1 malignant neurofibroma, 1 metastatic breast cancer, and 2 unknown cancers. DentaCT imaging was done with standard CT scans of the head and neck in all patients. One or more of MRI, panorex, bone scanning, and three-dimensional CT scans were obtained in a few of the patients.

Two of the patient group demonstrated neither

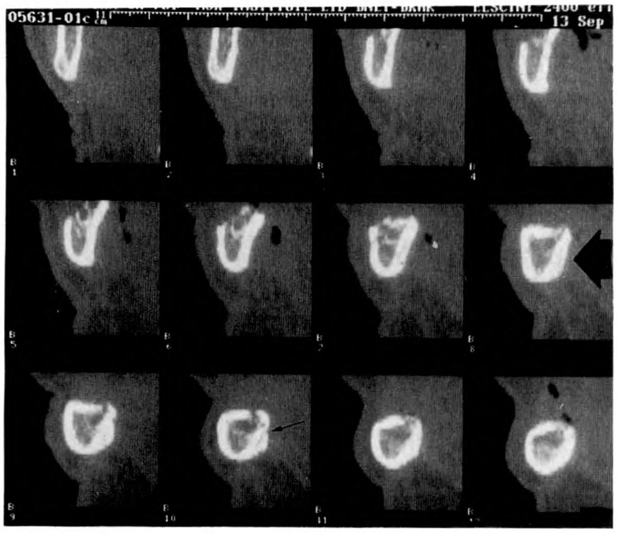

Fig 2. (Case 2) Periosteal reaction noted at lingual aspect of mandible (thick arrow). Thin arrow — area of periosteal disruption.

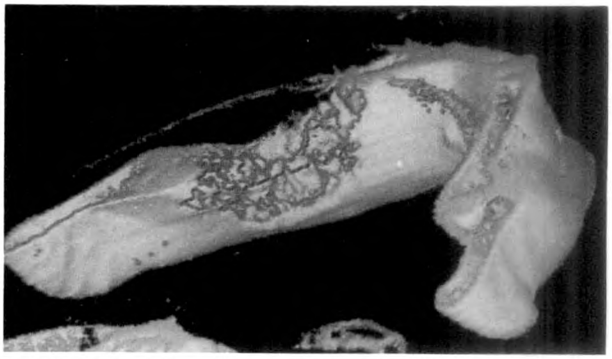

Fig 4. (Case 3) Three-dimensional computed tomography scan of lesion nicely depicts bony destruction, although its actual extent and depth are not readily defined by this imaging technique.

bony involvement nor involvement of the mandibular periosteum by histologic studies. This finding, as opposed to the clinical impression, was also indicated by their imaging. DentaCT imaging in all other 15 cases demonstrated obvious or minimal bony involvement that was confirmed in 12 patients who underwent surgery.

Eight cases are portrayed to illustrate the application of DentaCT imaging in head and neck oncology.

Case 1. A 73-year-old woman presented with persistent pain in her right preauricular region and stenosis of the external auditory meatus without trismus. Temporomandibular joint disorder was suspected and was treated. As pain persisted, DentaCT of the joint was obtained, clearly depicting severe destruction of the condylar head by tumor, later diagnosed as chondrosarcoma (Fig 1). The patient sought medical advice elsewhere and was lost to follow-up.

Case 2. A 78-year-old woman underwent resection of a T2 SCC of the lower lip with right modified neck dissection. One year later she underwent wide local excision of recurrent disease with myocutaneous flap reconstruction followed by radiotherapy. A tumorous mass was noted 1 year later in her right retromolar trigone area and biopsy confirmed recurrent SCC. A CT scan of the mandible demonstrated destruction of the buccal margin of the right angle of the mandible adjacent to the soft tissue mass. DentaCT confirmed these findings (Fig 2). The patient underwent wide local excision followed by brachytherapy, but succumbed to her disease 6 months later.

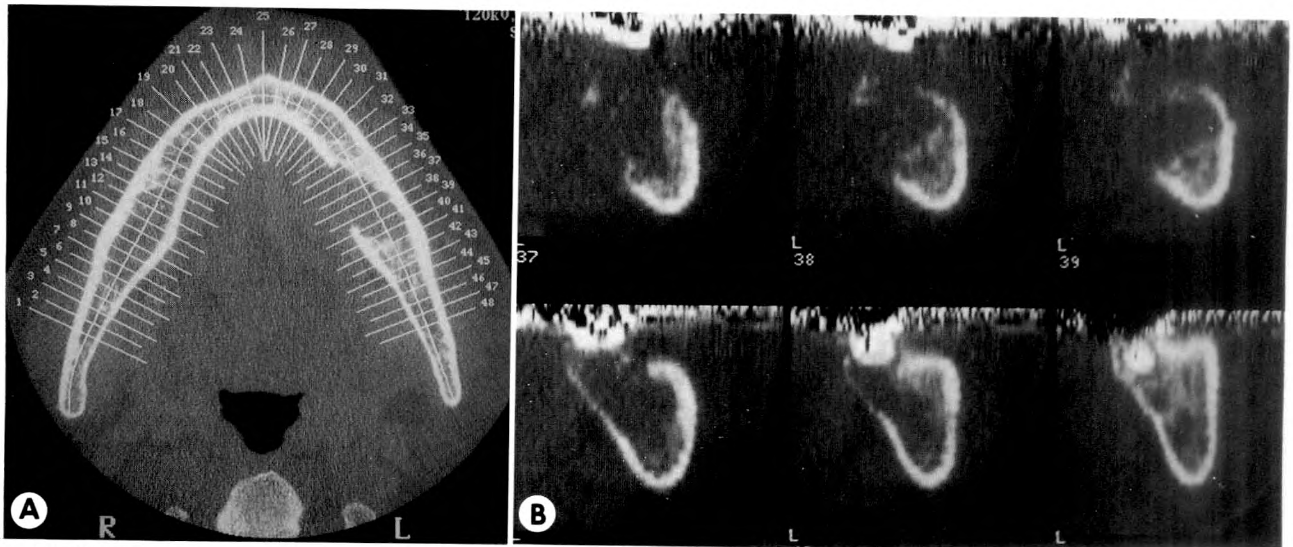

Fig 3. (Case 3) Large osteolytic lesion extending from second premolar to third molar tooth, with minimal involvement of mandibular canal and erosion of buccal cortical plate, is seen in DentaCT axial (A) and cross-sectional (B) views. Note superimposed central line on mandible with numbered perpendicular cross-lines corresponding with presented cross-sectional views.

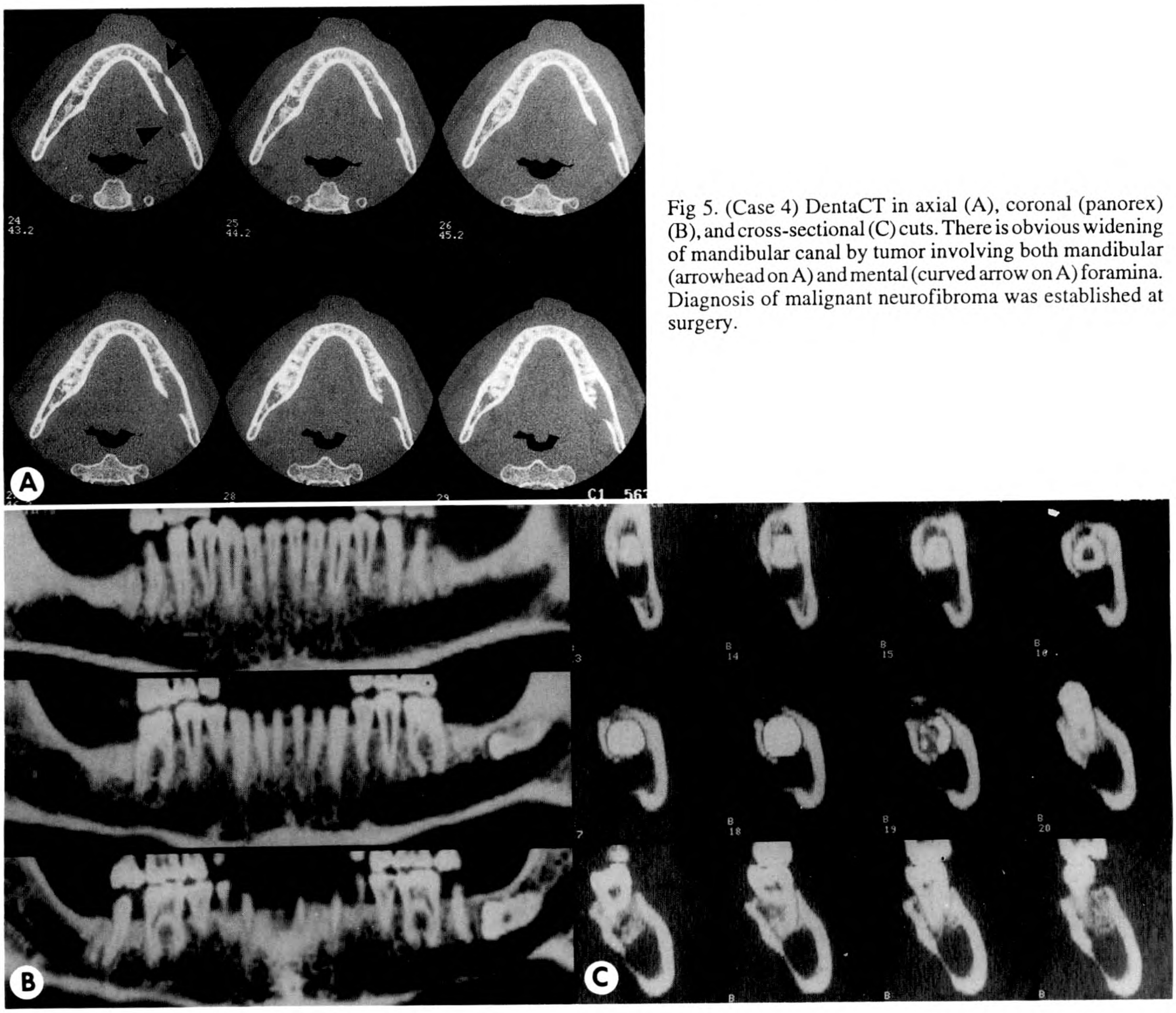

Fig 5. (Case 4) DentaCT in axial (A), coronal (panorex) (B), and cross-sectional (C) cuts. There is obvious widening of mandibular canal by tumor involving both mandibular (arrowhead on A) and mental (curved arrow on A) foramina. Diagnosis of malignant neurofibroma was established at surgery.

Case 3. A 79-year-old woman was referred for a nonhealing "dental abscess" in her left mandible of 2 weeks' duration. Physical examination revealed a small tumor with intact mucosa adherent to the body of the left mandible without hypesthesia or anesthesia of the mental region. Imaging studies by DentaCT and three-dimensional CT scans (Figs 3 and 4) revealed a large osteolytic lesion extending from the second premolar tooth to the third molar tooth with minimal involvement of the mandibular canal and erosion of the buccal cortical plate. The patient underwent wide excision with neck dissection and AO plate reconstruction followed by radiotherapy. A diagnosis of primary poorly differentiated SCC of the mandible was established.

Case 4. A 42-year-old man was admitted for a tumor of the left lower lip with hypesthesia of the left mental region. Biopsy revealed malignant schwannoma. DentaCT imaging was obtained, demonstrating marked widening of the left mandibular canal (Fig 5). This widening was also evident both in the mandibular and mental foramina. The patient later underwent wide resection with free iliac crest reconstruction. Permanent histologic studies were suggestive for malignancy arising in a neurofibroma.

Case 5. A 62-year-old woman was admitted for residual SCC of the left alveolar process with involvement of the ipsilateral maxillary sinus. Imaging studies obtained clearly depict the extent of the tumor in the maxilla and its invasion to the floor of the sinus (Fig 6).

Case 6. A 62-year-old man was admitted for treatment of an extensive SCC involving the lower lip with intraoral extension down to the gingivolabial sulcus with clinically highly suspected involvement of the mandible. DentaCT demonstrated only osteitis condensans without mandibular involvement, thus supporting a less aggressive surgical approach (Fig 7).

Case 7. A 77-year-old man was admitted for treat-

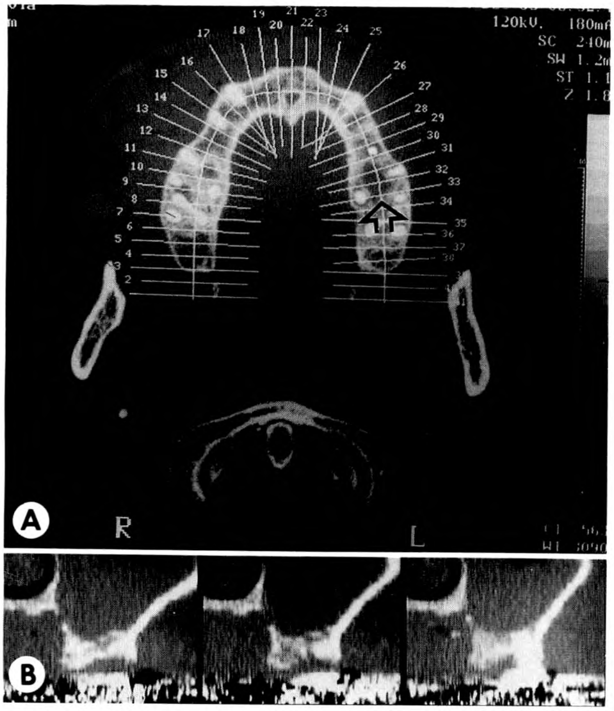

Fig 6. (Case 5) A) Axial DentaCT imaging portrays maxillary involvement by residual squamous cell carcinoma (arrow). B) Bone destruction (arrow) and soft tissue mass outline lower-medial border of left maxillary sinus. Star — inferior turbinate.

ment of a T2N1M0 SCC of the oral cavity overlying the third molar area. Suspected mandibular involvement could not be ruled out by a panoramic x-ray study or conventional CT scans. Periapical films and DentaCT imaging established the absence of bone involvement, which was confirmed by histologic studies. Marginal mandibulotomy was performed along with resection of the tumor and a modified radical neck dissection. Precise measurement of the location of the mandibular canal by DentaCT imaging assisted in allowing adequate resection of the mandibular rim in the atrophied mandible without damage to the inferior alveolar nerve.

Case 8. A 47-year-old woman was referred for a nonhealing tooth extraction site at the area of the molar teeth on the left mandible. On examination a "floating" second molar was seen and a 2-cm ipsilateral neck mass was palpated in level II. Tissue biopsy revealed SCC staged as T3N1M0. DentaCT imaging demonstrated partial destruction of the mandible and its lingual plate of the cortex at the soft tissue tumor site (Fig 8). Cross-sectional imaging clearly depicts the underlying mandibular destruction with the dislodged tooth. The patient underwent a composite resection and reconstruction followed by radiotherapy.

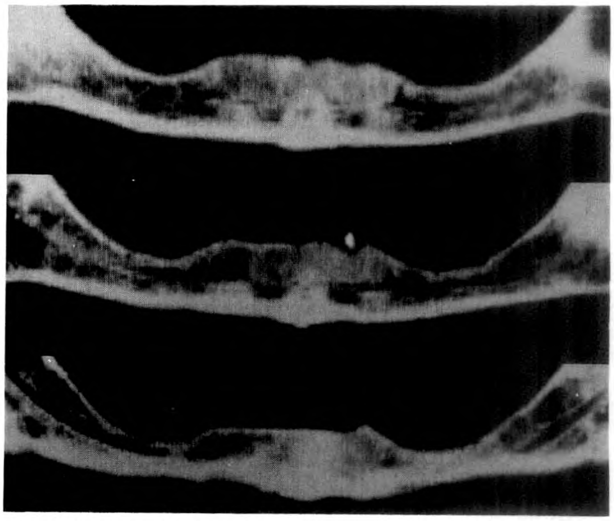

Fig 7. (Case 6) Reconstructed panorex DentaCT imaging demonstrates only osteitis condensans at symphysis area of mandible. Although clinically suspect of invasion with tumor, no involvement was found in surgical specimen.

DISCUSSION

DentaCT is a relatively new computer software package for CT, originally intended for assisting oral surgeons in dental prosthesis implantation (Elscint Ltd). DentaCT and DentaScan[3,4,9] are both MPR programs, permitting visualization of the mandible and maxilla in three planes — axial, oblique-sagittal (cross-sectional), and panoramic — and allow cross-sectional views of internal structures such as the maxillary sinuses and the incisive and inferior alveolar canals. A computer-drawn line superimposed on the center of the mandible serves as a reference for the reformatted cross-sectional and panorex images (Figs 3A and 6A). Perpendicular numbered lines correspond to the cross-sectional images, and a 1:1 scale in each of those allows precise measurement of dimensions and location of intraosseous structures.[10]

The contour, height, thickness, and mineralization of bone along the entire jaw curvature can be precisely defined. The oblique-sagittal or cross-sectional view, unique to this type of program, allows an unobstructed view of the buccal and lingual cortical margins. No further hindrance of osseous structures by superimposition is encountered.

We did not compare MRI and DentaCT and cannot state which is superior in our group of patients, although it was reported that DentaScan provides a better detailed cortical resolution and a panorex image not available with MRI.[3] Also, although DentaCT is a highly sophisticated software package, it is based on a CT scanner, and could be more available to small or medium-sized institutions than an MRI facility.

Our series of bone-invasive cases is limited, but there were no false-negative or false-positive results in the patients who underwent surgery. It should be noted, however, that although we had 2 cases in

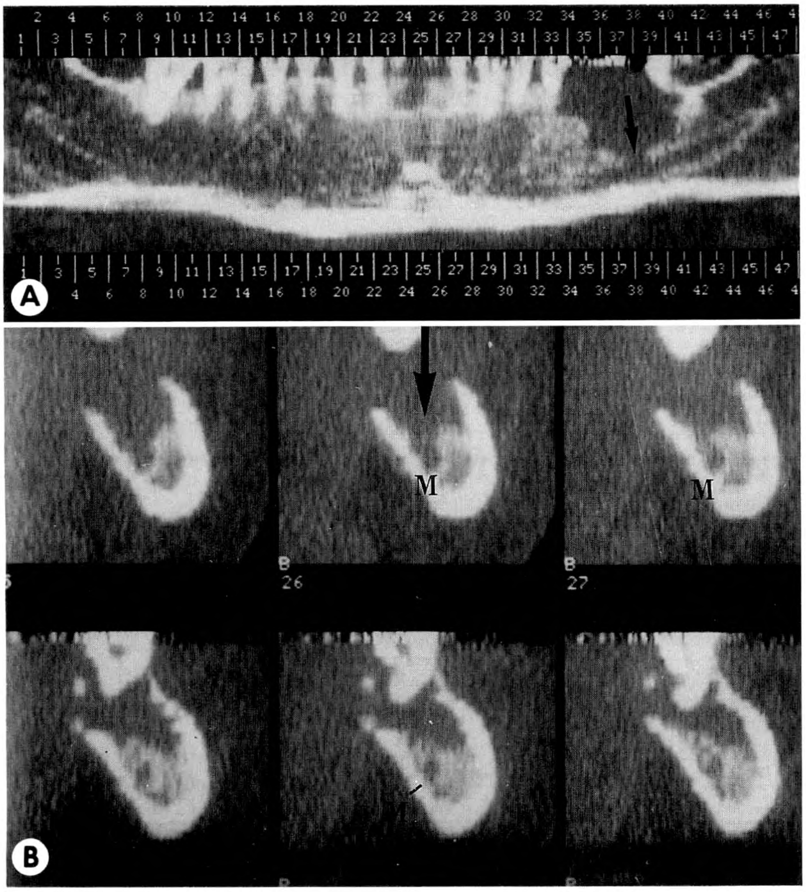

Fig 8. (Case 8) A) Panorex and B) cross-sectional DentaCT imaging demonstrates irregular lytic lesion surrounding roots of teeth 36 and 37. Erosion of superior border of mandibular canal (M) is evident (arrows). Note that cross-sectional cuts correspond anatomically but are numbered according to axial cut and are therefore discordant with presented panorex imaging.

which invasion was ruled out by imaging and this was corroborated by histologic studies, we did not scan patients in whom there was no clinical suspicion of bony involvement and therefore have no cases in which DentaCT pointed to a formerly nonsuspected invasion. In 1 patient (case 5) further bony extension into the maxillary sinus was found in addition to clinically evident alveolar ridge invasion. In all other cases, bony involvement was evident and DentaCT was useful mainly in delineating the tumor and establishing its extent in bone rather than ascertaining its actual involvement.

Bodner et al[10] describe their favorable experience in use of DentaCT in evaluating cystic jaw lesions. In the available reports,[4,9] a total of 22 cancer cases were evaluated by DentaScan. Although global patient data were not made available, it should be noted that the majority of the cancer cases described were of patients with recurrent tumors in whom bone involvement was, perhaps, more pronounced than in newly diagnosed cases of similar staging.

By surmounting shortcomings of conventional CT scanning such as disruption of images by metal artifacts and inability to produce true cross-sectional imaging, this modality is gaining popularity where available, with results described as advantageous[9] to superior.[4] DentaCT films are provided with a 1:1 scale ratio, allowing accurate and effortless measurement of distances and tissue dimensions. No additional radiation is necessary to produce this imaging, as it is computer-generated on available conventional CT data. DentaCT imaging is only marginally more time-consuming to produce and is available to us at costs no higher than those of conventional CT in our imaging facility — further support for use of this application.

Future studies comparing MRI to DentaCT should be undertaken in order to determine which is more efficacious in evaluating mandibular and maxillary disease and, in particular, which is better in establishing bony involvement. It could well be that the two modalities are complementary and their mutual use may become the gold standard for diagnostic imaging of invasive cancer of the oral cavity.

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FUNCTIONAL ENDOSCOPIC SINUS SURGERY: BASIC AND ADVANCED TECHNIQUES

The course Functional Endoscopic Sinus Surgery: Basic and Advanced Techniques will be held in Graz, Austria. The English course will be held July 11-13, 1996, and the German course September 5-7, 1996. For further information, contact Prof H. Stammberger, MD, ENT Department, University Hospital, Auenbruggerplatz 20, A-8036 Graz, Austria; fax ++43 316 385 3425.

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SUBTOTAL CARBON DIOXIDE LASER ARYTENOIDECTOMY BY ENDOSCOPIC APPROACH FOR TREATMENT OF BILATERAL CORD IMMOBILITY IN ADDUCTION

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Subtotal carbon dioxide (CO2) laser arytenoidectomy for endoscopic treatment of bilateral immobility of the vocal folds in adduction is a variant of total arytenoidectomy. The principal modification involves preservation of a thin posterior shell providing good postoperative fixation of the arytenoid region. The risk of aspiration is thus averted and collapse of arytenoid mucosa into the larynx during inspiration is prevented. The risk of synechia with the posterior commissure is avoided. The CO2 laser is operated at a working distance of 400 mm with a continuous 7-W beam in superpulse mode. Operation time is thus reduced to approximately half an hour and the risk of postoperative edema is reduced. Tracheotomy is not necessary. Forty-one patients, including 16 men and 25 women, were treated by this technique between 1985 and 1994. Their mean age was 55 ± 17 years, ranging from 11 to 83 years. Follow-up ranged from 1 month to 111 months (9 years 3 months), with a mean of 56 ± 29 months (4 years 8 months). The mean peak forced expiratory flow–peak inspiratory flow ratio (normal = 1), which permits a measurement of respiratory quality, is improved from 3.7 ± 1.4 preoperatively to 1.6 ± 0.5 postoperatively ($p < .001$). Postoperative voice measurements show a mean vocal intensity of 61 ± 3 dB hearing level, a mean maximum phonation time of 8 ± 4 seconds, and a mean phonation quotient of 397 ± 150 mL/s. As for vocal quality, 38% of the patients now have a near-normal voice according to our high-resolution frequency analysis, and all of the patients retained satisfactory voice quality.

KEY WORDS — bilateral vocal fold immobility in adduction, carbon dioxide laser, subtotal arytenoidectomy.

INTRODUCTION

Bilateral immobility of the vocal folds in adduction very often creates severe respiratory distress. The dyspnea is characteristically accompanied by good conservation of voice quality. The management of this problem involves searching for a compromise between socially satisfactory phonation and an airway compatible with an active life.

The treatment of immobility of the folds in adduction has evolved with time. Prior to 1922 there was no alternative to tracheotomy. In 1922, Chevalier Jackson[1] reported on ventriculocordectomy, which restored a satisfactory airway but permitted only a weak whispered voice. In 1932, submucosal resection of a vocal fold was proposed by Hoover,[2] but this often creates secondary fibrous glottic retraction. In 1939, extralaryngeal arytenoidectomy was introduced by King.[3] The procedure is based on the freeing of the arytenoid cartilage from all its muscular and ligamentar attachments except the vocal muscle. The arytenoid is then fixed laterally to the thyroid ala. Two years later, Kelly[4] performed extralaryngeal arytenoidectomy, which he improved by fixation of the corresponding vocal fold in order to conserve a good glottic opening. Modified arytenoidectomy was described by Woodman[5] in 1946 with lateralization of the ipsilateral vocal fold by submucosal suture of the preserved vocal process and fixation to the inferior horn of the thyroid cartilage. In 1955, Rethi[6] proposed a modified laryngoplasty. The intervention consisted of placing a cartilaginous fragment in position following posterior section of the cricoid. It is completed by an endolaryngeal stent. In 1968 Downey and Keenan[7] performed an arytenoidectomy via laryngofissure. In 1972, Helmus[8] ameliorated Downey and Keenan's technique through the use of an operative microscope.

The endoscopic approach for the treatment of vocal fold immobility was proposed in 1948 by Thornell,[9] who performed the first micro-instrumental arytenoidectomy by an endolaryngeal approach. In 1979, lateralization of the vocal fold by a suture via the endoscopic route was proposed by Kirchner.[10] In 1972, Strong et al[11] inaugurated the use of the carbon dioxide (CO2) laser in laryngeal surgery and were, in 1976, the first to mention the use of the CO2 laser for arytenoidectomy by the endoscopic route.[11] In 1983, Eskew and Bailey[12] published a report on arytenoidectomy by an endoscopic approach with the CO2 laser in dogs. That same year, Ossoff et al[13] reported the first four CO2 laser arytenoidectomies by the

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TABLE 1. DEMOGRAPHIC DATA

N	41
Female	25
Male	16
Age (y)	
Mean ± SD	55 ± 17
Minimum	11
Maximum	83
Follow-up (mo)	
Mean ± SD	55 ± 29
Minimum	1
Maximum	111
Paralysis	26
Thyroidectomy	17
Tumoral compression	4
Viral neuritis	2
Esophagectomy	1
Tracheal surgery	1
Peripheral neuropathy	1
Ankylosis	15
Intubation	8
Radiotherapy	3
Trauma	2
Inflammatory process	2
Patients already tracheotomized	8

endoscopic route, successfully performed in patients with laryngeal diplegia in adduction. In 1984, they published a series of 11 patients, of whom only 1 developed a posterior "web."[14] In 1985, Remsen et al[15] proposed an excision of the thyroarytenoid muscle by the CO_2 laser associated with a suture for lateralization of the vocal ligament. Posterior cordectomy by the CO_2 laser via an endoscopic approach was performed by Dennis and Kashima[16] with satisfactory results as reported by the authors in a series of 6 cases. Crumley[17] proposed a minimal intervention consisting of notching the internal faces of the bodies of the arytenoid cartilages while sparing the vocal processes in cases in which recovery of mobility can be hoped for.

Attempts to restore mobility by reinnervation have been made. Thus, in 1976, reinnervation by insertion of a neuromuscular pedicle was proposed and successfully performed by Tucker,[18] but has not been adopted by other authors for the treatment of bilateral paralyses.

In 1977, Zealear and Dedo[19] demonstrated experimentally that electrical stimulation could trigger and drive the action of the laryngeal muscles.

On our part, we have opted for CO_2 laser arytenoidectomy by the endoscopic route. Our technique, which is derived from that of Ossoff et al,[20] is reported below for 41 patients.

MATERIALS AND METHODS

From March 1985 to June 1994, 41 patients were treated by subtotal arytenoidectomy for immobility of the vocal folds in adduction. The group was composed of 25 women and 16 men, with a mean age of 55 ± 17 years (median, 59; range, 11 to 83) at the time of the intervention. Twenty-six patients suffered from recurrent paralysis, of whom 17 had had thyroidectomy, 4 had had tumoral compression (pulmonary and esophageal neoplasm), 2 viral neuritis, 1 esophagectomy, 1 tracheal surgery, and 1 peripheral neuropathy. The 15 remaining patients suffered from bilateral cricoarytenoid ankylosis that was due to prolonged intubation in 8 cases, following radiotherapy in 3 cases, subsequent to an inflammatory process in 2 cases, and posttraumatic in 2 cases. Eight patients had undergone tracheotomy prior to their referral (Tables 1 and 2).

The intervention is carried out by laryngoscopy in suspension under general anesthesia. A No. 6 special laser endotracheal tube (Tube Laser Flex, Mallinckrodt, United Kingdom) or a classic tube protected by aluminum adhesive tape (tape from 3M, 3042G, Minneapolis, Minn) enables ventilation. In patients already tracheotomized, a No. 6 or 8 Shiley cannula, also protected by aluminum tape, is used for ventilation.

A Kramer laryngoscope (Wolf, Knittlingen, Germany) allows exposure of the arytenoid for resection. Neurosurgical cottonoids moistened with saline are introduced in order to protect the endotracheal tube balloon or the cannula. The balloon is inflated with normal saline tinted with methylene blue in order to reveal any possible damage during the course of the intervention. The patient's face is protected by large, moist compresses.

We employ a CO_2 laser (Sharplan model 1060, Laser Industries, Tel Aviv, Israel) adapted to an operative microscope (Wild, Wurburg, Switzerland). Double aspiration is essential, one aspiration connected to the laryngoscope and the other to an aspiration-coagulation tube. The surgical resection was initially performed at a power of 15 W, in continuous focused mode. Since 1989, we have used the superpulse mode at a power of 7 to 8 W.

The procedure (Fig 1) starts with section between the vocal process and the membranous part of the vocal fold. The section must be completed in order to obtain retraction of the membranous vocal fold to the front. Thereafter, the section extends to the posterior ventricular fold to reach the external part of the arytenoid.

The section includes the laryngeal slope of the

TABLE 2. BREAKDOWN OF PATIENTS ACCORDING TO CAUSE OF IMMOBILITY AND FOLLOW-UP

Patient	*Sex*	*Age (y)*	*Diagnosis*	*Cause*	*Follow-up (mo)*
1	F	67	Paralysis	Thyroidectomy	111
2	F	63	Paralysis	Thyroidectomy	102
3	M	50	Ankylosis	Radiotherapy	102
4	F	77	Paralysis	Tracheal surgery	100
5	F	56	Paralysis	Thyroidectomy	91
6	M	56	Paralysis	Esophageal cancer	91
7	F	61	Paralysis	Thyroidectomy	89
8	M	59	Ankylosis	Radiotherapy	83
9	M	43	Ankylosis	Intubation	80
10	M	70	Paralysis	Lung cancer	80
11	M	61	Ankylosis	Intubation	79
12	F	57	Paralysis	Thyroidectomy	78
13	F	50	Paralysis	Thyroidectomy	78
14	F	63	Paralysis	Thyroidectomy	66
15	M	51	Paralysis	Esophagectomy	64
16	F	60	Ankylosis	Intubation	62
17	F	60	Paralysis	Thyroidectomy	60
18	M	74	Paralysis	Thyroidectomy	57
19	F	39	Paralysis	Thyroidectomy	54
20	M	64	Paralysis	Thyroidectomy	51
21	F	70	Paralysis	Tracheoesophageal cancer	51
22	F	58	Paralysis	Thyroidectomy	51
23	F	77	Ankylosis	Trauma	48
24	F	74	Paralysis	Viral neuritis	48
25	M	67	Paralysis	Thyroidectomy	47
26	M	39	Ankylosis	Intubation	47
27	F	60	Ankylosis	Inflammatory process	46
28	M	59	Ankylosis	Intubation	45
29	F	37	Ankylosis	Radiotherapy	45
30	M	11	Ankylosis	Intubation	43
31	M	67	Paralysis	Viral neuritis	42
32	F	26	Ankylosis	Trauma	39
33	F	51	Paralysis	Thyroidectomy	30
34	F	83	Paralysis	Thyroidectomy	27
35	F	33	Ankylosis	Intubation	24
36	F	50	Ankylosis	Inflammatory process	17
37	F	12	Ankylosis	Intubation	13
38	F	38	Paralysis	Thyroidectomy	9
39	F	37	Paralysis	Thyroidectomy	9
40	M	35	Paralysis	Lung cancer	1
41	M	70	Paralysis	Peripheral polyneuropathy	1

arytenoid. The pharyngeal slope, as well as a superior border of 2 to 3 mm, is spared. The posterior commissure must be protected very carefully to avoid any secondary synechiae. This protection is usually obtained, thanks to the ventilation tube filling this commissure.

The section of the arytenoid cartilage body is a very important stage of the procedure. A 2-mm posterior shell of the arytenoid cartilage must be preserved. In doing so, the muscular process is also respected. This section is more easily performed in superpulse mode because of its superior sectioning effect with less carbonization, which can mask the limits of the tissues to be spared. Conservation of the posterior shell can be ensured by mobilizing the arytenoid mucosa all around. If the posterior shell looks too thick, it can be made thinner by vaporization.

The procedure is completed by splitting of the joint between the cricoid cartilage and the resected part of the arytenoid cartilage body. Total resection of the body of the arytenoid can be ensured by mobilizing

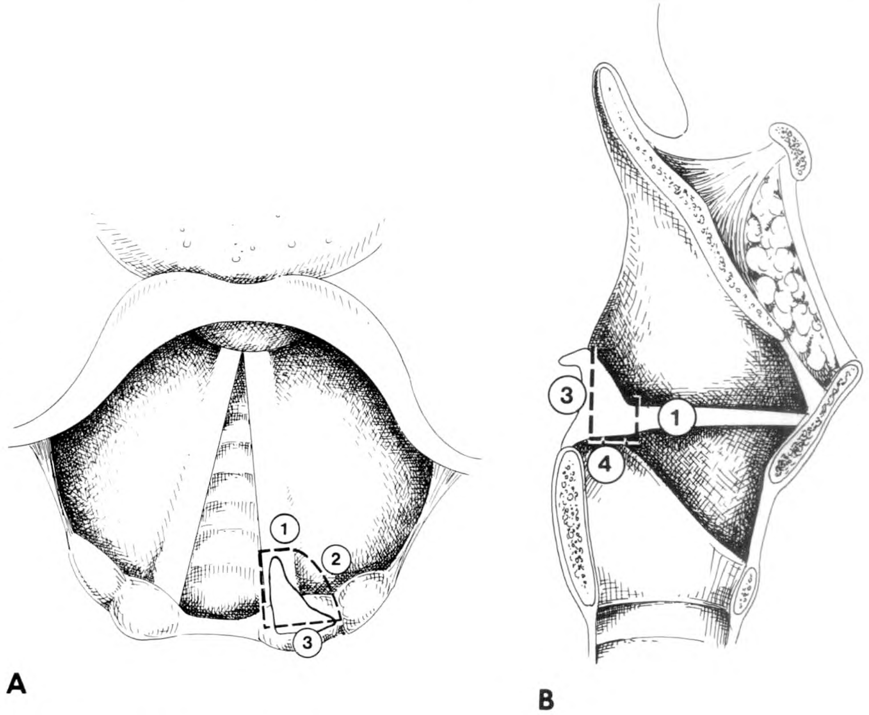

Fig 1. Limits of subtotal arytenoidectomy. 1 — Section of vocal process from membranous part of vocal fold; 2 — section of posterior part of ventricular fold; 3 — section of arytenoid cartilage with preservation of posterior shell; 4 — split between arytenoid cartilage and cricoid cartilage. A) Superior view. B) Sagittal view.

the cricoid cartilage from bottom to top in front of the posterior arytenoid shell, which has been preserved. This mobilization of the cricoid, carried out with microforceps, leads to the mobilization of the entire larynx. If necessary, hemostasis of the arytenoid artery is obtained by electrocoagulation via the aspiration-coagulation tube (Wolf).

The surgical procedure lasts 25 to 30 minutes. The resection zone of the arytenoid is covered with a thin layer of slow-setting fibrin glue (Tissucol, Immuno, Vienna, Austria). This layer of fibrin glue prevents the formation of granulomas and decreases diffuse postoperative bleeding as well as crust formation. This fibrin glue, made of pooled blood products, is currently used in Europe but is not approved by the US Food and Drug Administration. During surgery, antibiotics (cefazolin sodium 1 g) and steroids (hydrocortisone sodium succinate 100 mg) are administered intravenously.

Upon awakening, nontracheotomized patients are extubated in the operating room. In case of respiratory difficulties due to edema, the patient is reintubated and observed for 24 hours in the intensive care unit. Extubation is carried out under visual control. Tracheotomized patients are decannulated between the 10th and the 15th days, after a test weaning (No. 4 Shiley cuffless cannula occluded for 48 consecutive hours). All patients received postoperative therapy including broad-spectrum antibiotics for 6 to 10 days, aerosol therapy (alternating corticosteroids and antibiotics), and constant humidification of the hospital room. Speech therapy is undertaken after about 10 days.

Respiratory function measurement was based on the ratio of peak forced expiratory flow to peak inspiratory flow (PEF/PIF ratio; normal = 1).

Vocal results were evaluated by high-resolution frequency analysis of the voice (Bruel and Kjaer 2033, Naerum, Denmark) according to criteria already defined.[21,22] The vocal frequency analysis is recorded in the form of a histogram of intensity as a function of frequency: type 0, practically flat trace (absence of sound); type 1, absence of the peaks corresponding to the fundamental frequency and harmonics; type 2, presence of noise (presence of the fundamental frequency; the peaks corresponding to the harmonics are absent or rudimentary); type 3, persistence of noise (the peaks corresponding to the fundamental frequency and to the harmonics remain widened and notched); and type 4, normal trace (absence of noise; the peaks corresponding to the fundamental frequency and harmonics are present). Other vocal measurements include intensity (decibels hearing level), maximum phonation time (seconds), and phonation quotient (milliliters per second).

Numeric values are expressed as means ± SD and medians. Preoperative and postoperative PEF/PIF ratios were compared by using a paired Student's *t*-test. For this variable, the correlation between the improvement and the preoperative value was assessed by the Pearson correlation coefficient, and by

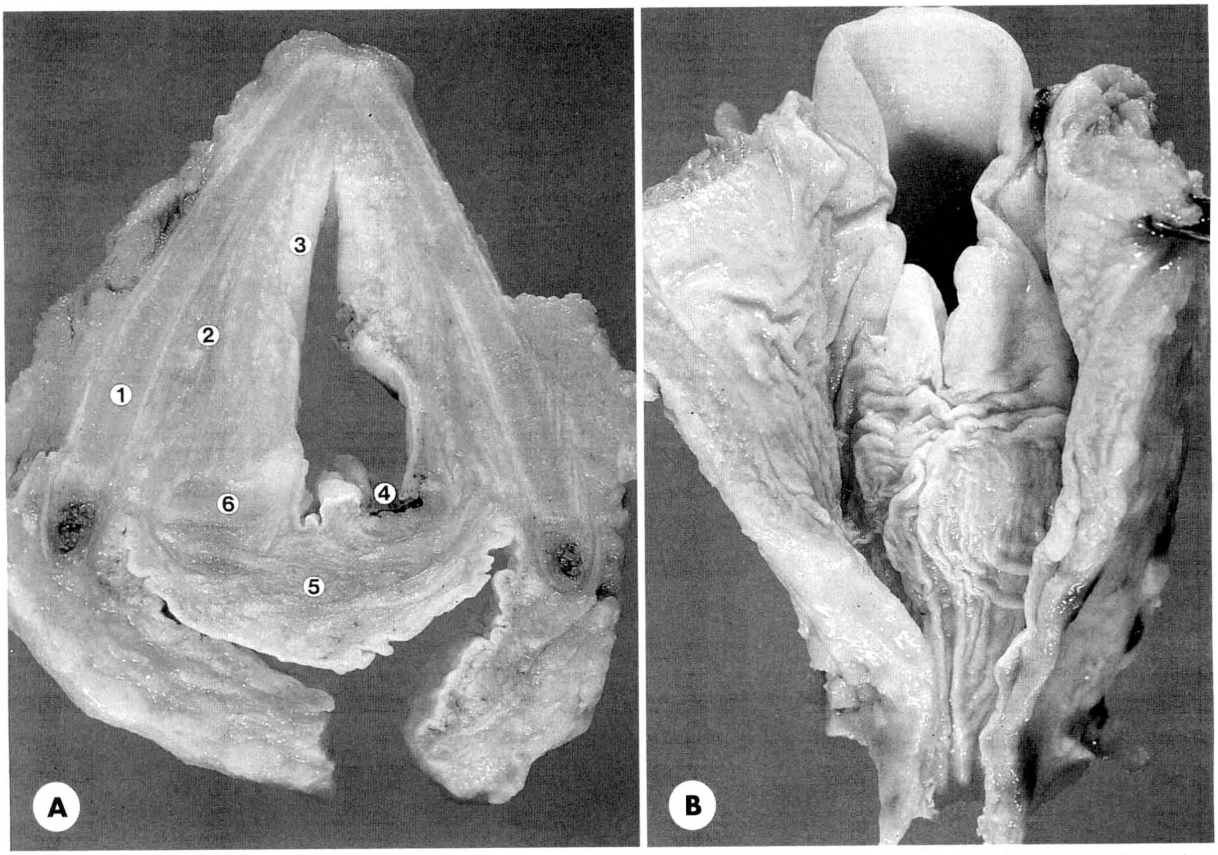

Fig 2. Postarytenoidectomy larynx (postmortem anatomic specimen from patient 40). A) Horizontal section. 1 — Thyroid cartilage; 2 — thyroarytenoid muscle; 3 — vocal ligament; 4 — posterior arytenoid shell; 5 — posterior commissure; 6 — arytenoid cartilage. B) Posterior view.

the Oldham method to remove bias due to such an artificial correlation.[23]

RESULTS

As far as the intervention is concerned, 40 of the 41 patients had a favorable course. One patient had a posterior synechia due to nonpreservation of the posterior commissure. The 8 patients who had undergone tracheotomy prior to their referral were successfully freed from the cannula within 15 days. The best vocal rehabilitations were obtained in cases of paralysis of the Gerhardt type, because of the sparing of adduction capability with preservation of tone quality and of pitch. Usually there are several episodes of aspiration of liquids, rapidly compensated after the first postoperative days. Nevertheless, in 5 patients there were aspirations, primarily involving liquids, with progressive involvement spread over 5 to 30 days. Three patients were unable to return to normal food intake because of intercurrent esophageal tumor. We also observed 2 cases of granulomas that spontaneously improved. Cicatrization time varied from 15 to 25 days. One patient (No. 40; Fig 2) died within 1 month after surgery of carcinomatous lymphangitis.

The postoperative follow-up in our series ranges from 1 month to 111 months (9 years 3 months), with an average of 56 ± 29 months (4 years 8 months) and a median of 51 months (Table 1). All patients have maintained a sufficient and stable respiratory airway, compatible with an active life (stair-climbing, housekeeping) without excesses. The PEF/PIF ratio was obtained on 25 patients postoperatively and on 13 patients preoperatively and postoperatively (Table 3). Its measurement is not available for all the patients because some patients were referred in emergencies or already tracheotomized or even intubated. They were sometimes transferred back to their hospitals after the procedure. The mean value for the PEF/PIF ratio calculated on the 13 patients is 3.7 ± 1.4 (median, 3.3) preoperatively and 1.6 ± 0.5 (median, 1.6) postoperatively, the difference being statistically significant ($p < .001$).

Moreover, the magnitude of improvement of this ratio was significantly correlated with the preoperative values ($r = .925$ and $p < 10^{-5}$, with $r = .759$ and $p = .003$ for the corrected coefficient according to Oldham), showing that the higher the preoperative value, the better the improvement.

Voice measurements have been realized on the 13

TABLE 3. PEF/PIF RATIO BEFORE AND AFTER SURGERY

Patient (n = 25)	*Before*	*After*
2		3.5
3		3.9
7		1.6
12		2.0
14		1.2
16	4.0	1.9
17		2.4
19	3.6	2.4
21	3.0	1.8
22	4.5	1.8
24		2.2
25	7.1	1.6
26	3.1	2.0
27	5.0	1.0
29		1.7
30	2.6	1.1
32	1.9	1.2
33	4.8	2.7
34		1.0
35	3.3	1.4
36	2.9	1.0
37		1.2
38	2.2	1.2
39		1.3
41		1.0

PEF — peak forced expiratory flow, PIF — peak inspiratory flow.

TABLE 4. VOCAL ASSESSMENT FOLLOWING SUBTOTAL ARYTENOIDECTOMY

Patient (n = 13)	*Frequency Analysis* (Type)*	*Mean Vocal Intensity (dB HL)*	*Maximum Phonation Time (s)*	*Phonation Quotient (mL/s)*
7	3	60	8	697
14	3	68	12	356
22	3	62	7	350
25	3	62	3	121
26	3	64	10	359
29	4	60	18	218
30	4	64	9	395
32	4	59	9	275
33	1	56	4	458
35	4	58	10	376
36	2	57	4	500
38	3	60	6	640
39	4	59	10	420

*See text for definition of types.

patients we followed ourselves on a long-term basis (Table 4). Regarding the frequency analysis, we found a graph similar to the one of a normal voice (type 4) in 5 patients (38%), of good quality in 6 patients (46%), of fair quality in 1 patient (8%), and of poor quality in 1 patient (8%). Mean values were as follows: intensity 61 ± 3 dB hearing level (median, 60), maximum phonation time 8 ± 4 seconds (median, 9), and phonation quotient 397 ± 150 mL/s (median, 376).

DISCUSSION

Subtotal arytenoidectomy such as we propose is performed by an endoscopic approach in 25 to 30 minutes and does not require a prior tracheotomy. The superpulse mode, by increasing the cutting effect and by decreasing the thermic effect and the risk of edema, avoids tracheotomy in these patients. So far, following our laser parameters for this indication, we did not observe any postoperative edema requiring the patient to be reintubated or tracheotomized after leaving the operating room. However, if any edema is observed when the procedure is completed, contraindicating extubation, a prolonged intubation for 24 hours in the intensive care unit is sufficient to correct the problem. This has not happened since we have been using the superpulse mode.

The use of the CO2 laser renders the surgery incontestably easier than in the microinstrumental procedures. In addition, the laser permits bloodless surgery except at the level of the arytenoid artery, which is controlled by electrocoagulation. We did not observe any secondary bleeding with the risk of blood inhalation, either.

In the process of CO2 laser arytenoidectomy, the microspot (Acuspot, Sharplan Laser Industries) offers no advantage. Certainly, it is more precise from the point of view of the resection, but this is achieved at the expense of hemostasis, which remains an important stage of the intervention. The microspot therefore seems of little use and may actually be disadvantageous for endoscopic arytenoidectomy.

In modification of the technique described by Ossoff et al,[14] we propose a laser resection in continuous superpulse mode. The effectiveness of the cartilaginous dissection thus obtained considerably reduces the operation time as compared to working in conventional mode with repeat mode. The preservation of a posterior cartilaginous shell contributes to the formation of a kind of reinforced flap contributing to a better stability of the arytenoid region. We were able to obtain the laryngeal specimen from a patient who died of carcinomatous lymphangitis (patient 40), who had previously suffered from bilateral paralysis of the vocal folds in adduction. We had carried out a subtotal arytenoidectomy. Observation of the larynx from a posterior view and in axial section (Fig 2) permits a better understanding of the role of the arytenoid shell. Two advantages are obtained thanks to this reinforced flap: prevention of muscular-mucosal collapse, which would partially reduce the respiratory airway posteriorly, and contribution to the prevention of severe aspiration.

Posterior cordectomy, also performed with the CO2 laser by an endoscopic approach, has the advantage of a shorter operating time: around 10 minutes. It may be carried out in elderly patients or those in precarious general condition in whom briefness of narcosis has great importance. However, the improvement in the respiratory airway may turn out to be insufficient, especially during moderate effort. Surgical reintervention for early (6 to 8 weeks) airway insufficiency or for postcicatrization fibrosis has indeed been reported by Dennis and Kashima.[16]

Application of fibrin glue at the site of the resection seems to us to be an additional safety factor. It must be applied sparingly, at approximately 0.5 mL. It is important to use slow-setting fibrin glue with a low concentration of thrombin (4 IU of thrombin per milliliter of glue). The setting time is about 1 minute. The rapid-setting glue does not favor proper application, as it can form a large mass that may be expelled during coughing effort, or worse, inhaled by the patient. On the other hand, the slow-setting glue allows a thin film to spread over the entire zone of resection.

Subtotal arytenoidectomy by the endoscopic approach allows prevention of intervention by the external route with satisfactory results. The duration of the intervention is markedly shortened, the postoperative period is easier for the patient, and the hospitalization is shorter.

Regarding respiratory function, the results are significantly better after the procedure and the improvement is statistically more important if the preoperative PEF/PIF ratio is high. Nevertheless, our results might have been even better if we had been able to test the preoperative PEF/PIF ratio of the most severe cases, which required an emergency procedure or even tracheotomy or intubation before operation.

Preservation, as much as possible, of the vibrating portion of the vocal fold during the subtotal arytenoidectomy can improve preservation of voice quality. But, of course, this procedure is a compromise between voice and breathing. Speech therapy is recommended in order to improve the voice as much as possible after this procedure. The best results are observed in Gerhardt's syndrome, thanks to the still-possible adduction.

One can criticize our phonatory measurements, mainly the phonation quotient. Measurements of the mean flow rate could have been more accurate, but special equipment is required for its measurement. This equipment is still uncommon in Europe and not available at the present time in our department. In contrast, the phonation quotient is easily obtained by any speech therapist.

CONCLUSION

Carbon dioxide laser subtotal arytenoidectomy by the endoscopic route, derived from classic arytenoidectomy according to Ossoff et al,[14] seems to us to be an interesting alternative. Thanks to preservation of a cartilaginous posterior shell supporting the muscular-mucosal arytenoid flap, it ensures stable respiratory results and contributes to the prevention of severe aspiration. Preservation of the vibratory portion of the vocal fold contributes to better vocal recuperation.

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MIDDLE EAR MECHANICS IN RESEARCH AND OTOSURGERY

The international workshop Middle Ear Mechanics in Research and Otosurgery will be held in Dresden, Germany, September 19-22, 1996. For further information, contact Prof Dr K. B. Hüttenbrink, Universitäts-HNO-Klinik, Fetscherstr 74, 01307 Dresden, Germany; telephone (Germany) (0)351-458-2224; fax (0)351-458-4326.

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VALUE OF ELECTROMYOGRAPHY IN DIFFERENTIAL DIAGNOSIS OF LARYNGEAL JOINT INJURIES AFTER INTUBATION

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Laryngeal joint injury or arytenoid dislocation is not an uncommon complication resulting from intubation trauma, and is best evaluated by laryngeal electromyography (EMG) combined with laryngoscopic examinations. Two cases of cricoarytenoid joint injuries after intubation are reported along with laryngeal EMG findings. Early diagnosis of arytenoid dislocation is important for appropriate surgical management and better prognosis. However, the reported cases, because of delayed referrals, showed prolonged cricoarytenoid joint injuries associated with thyroarytenoid muscle denervation or myopathy, and resultant vocal fold immobility. The results of laryngeal EMG in cricoarytenoid joint injuries can be classified into three different patterns: 1) normal recruitment, 2) myopathy, and 3) denervation or reinnervation of the thyroarytenoid muscles. It is particularly valuable to sample different portions of the thyroarytenoid muscles with EMG in order to evaluate different patterns or pathologic changes of the muscles and nerve paralysis.

KEY WORDS — arytenoid dislocation, intubation, laryngeal electromyography, videostroboscopy.

INTRODUCTION

Voice disorders following tracheal intubation or gastric intubation are frequently seen in clinical practice.[1,2] Direct laryngoscopy at time of extubation shows that 94% of patients suffer from laryngeal damage due to prolonged intubation, including mucosal ulceration along the posterior-medial aspects of both vocal folds.[3,4] The incidence of short-term intubation in association with vocal fold immobility is reported to be 6%[5] and 30%.[6] Early differential diagnosis and management of voice disorders and vocal fold immobility are particularly important for better recovery and prognosis. However, clinicians are often unclear about whether intubation-induced vocal fold immobility is caused by laryngeal nerve injuries or laryngeal joint damage or dislocation, if they only rely on laryngoscopic examinations. It is reported that bilateral arytenoid disolocation can be complicated by acute respiratory distress after tracheal extubation.[7] Delayed management of arytenoid dislocation may result in cricoarytenoid joint ankylosis, a major sequela of joint injury by intubation. Subsequent muscular denervation and laryngeal injury may develop and produce long-term complications such as dysphonia and choking. Vocal fold immobility may be classified as vocal fold paralysis or cricoarytenoid joint dislocation. Clinicians should be alert to these possibilities when patients present with hoarseness, breathiness, pain on phonation or swallowing, and respiratory dyspnea after extubation. A routine laryngeal examination should be conducted promptly, including nasopharyngoscopy or videostroboscopy.

The diagnosis of dislocation or subluxation of the laryngeal joints, in general, is made by a typical history of intubation and laryngoscopic examinations. Some authors have provided documents of computed tomography (CT) regarding its value in diagnosis of arytenoid dislocation.[5] However, because of insufficient mineralization of the cricoarytenoid joints, CT imaging may not be useful in some patients, especially those younger than 15 years. In addition, CT provides little information regarding the functional status of the cricoarytenoid muscles relating to arytenoid dislocation. Laryngeal joint injury or arytenoid dislocation is therefore best evaluated by laryngeal electromyography (EMG) combined with laryngoscopic examinations. Laryngeal EMG is essential in differentiating between vocal fold paralysis and arytenoid dislocation. The term vocal fold immobility should be used to describe the situation in which decreased or absent movement of the vocal folds is associated with asymmetric arytenoids in position as shown on laryngoscopic examination prior to EMG. Unfortunately, investigations of laryngeal joint injuries by means of laryngeal EMG are not well documented. This case study is presented for discussion of the diagnostic value of laryngeal EMG in further interpretation of the mechanism of laryngeal injury following extubation. The techniques and patterns of laryngeal EMG will be discussed.

CASE REPORTS

Case 1. A 29-year-old woman presented to our

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clinic with a 21-day history of hoarseness and choking following extubation after 2 months of intubation for pulmonary infection and dyspnea. She complained of sore throat, choking, and difficulty swallowing.

The patient arrived in a wheelchair. General examination showed mild dyspnea and harsh voice quality. The patient was found to have an intravenous catheter on the right side of the neck. Laryngeal videostroboscopy showed that the left vocal fold moved normally with decreased movement of the right vocal fold. Marked swelling was noted on the right arytenoid area. The tip of the vocal process of the right arytenoid appeared to be displaced anteriorly and inferiorly with resultant lateral displacement. Both vocal folds showed edema. The mucosal wave was decreased on the left vocal fold and absent on the right vocal fold. Incomplete closure of the glottis was revealed when the patient was instructed to phonate with maximal effort.

Case 2. A 27-year-old woman presented with a 4-month history of hoarseness after tracheal intubation performed during bilateral intraoral mandibular vertical ramus osteotomies. She also complained of mild coughing that occurred when she ate.

General examination revealed normal respiration status and a breathy and harsh voice quality. Laryngeal videostroboscopy showed left vocal fold immobility in the paramedian position with normal movement of the right vocal fold. The arytenoids were asymmetric in position with reddish mucosal membrane in the region of the left arytenoid cartilage. The left arytenoid was suspected to have anterior and inferior dislocation.

ELECTROMYOGRAPHY PROCEDURES AND RESULTS

Laryngeal EMG was conducted on both patients. Bilateral EMG signals were recorded with the Spirit evoked potential system (Nicolet Co). A surface ground electrode was placed on the skin of the sternum, and a pair of disposable adhesive electrodes were placed on the skin of the sternocleidomastoid muscle at the level of the cricothyroid space, where the electrodes were inserted. The skin was first anesthetized with 4% lidocaine. The bipolar concentric electrode was then inserted into the cricothyroid space plane, passing by the cricothyroid ligament. When the electrode was passed through the skin and the cricothyroid membrane, it was directed up approximately 45° superiorly and 35° to 40° laterally to insert into the thyroarytenoid muscle. The EMG signals were recorded during the patient's quiet respiration and phonation from the monitoring waveforms on the screen and sound from a loudspeaker. The patient was instructed to abstain from swallowing and say /ee/ during the examination.

The patient in case 1 sat in a wheelchair with extension of her neck. The left vocal fold with normal movement was tested first, followed by the right vocal fold. To sample different portions of the right thyroarytenoid muscle, the electrode was first inserted about 2 cm in depth to approach the middle portion, then inserted 1 cm further to reach to the posterior portion. Finally, the electrode was pulled back into the anterior portion. The patient in case 2 lay on an examination table. Both cricothyroid muscles and thyroarytenoid muscles were sampled.

In case 1, bilateral simultaneous recordings of EMG from the thyroarytenoid muscles with concentric electrodes showed that there was a recruitment pattern in the left vocal fold, but different patterns in the right thyroarytenoid were noticed in the three portions of the thyroarytenoids sampled. The anterior portion of the right thyroarytenoid muscle showed a normal recruitment pattern, while the middle portion appeared to have high-frequency discharge and some muscular activity related to phonation that indicated laryngeal myopathy to some degree (Fig 1). The lower amplitude of EMG and electric silence periods were found in the posterior portion of the right thyroarytenoid muscle, in contrast to the normal recruitment pattern in the left thyroarytenoid muscle (Fig 2). These results suggest that an incomplete closure of the glottis was more likely related to a local lesion caused by the intubation procedure. Thus, dislocation or subluxation of the right cricothyroid joint can be confirmed and needs surgical management. Laryngeal EMG in case 2 showed a normal recruitment pattern of the right cricothyroid and thyroarytenoid muscles and the left cricothyroid muscle. The patient's left thyroarytenoid muscle revealed positive sharp waves and polyphasic potentials, suggesting denervation and reinnervation (Fig 3).

DISCUSSION

The complication of arytenoid dislocation or subluxation or vocal fold paralysis following tracheal or gastric intubation is not rarely reported in the literature.[7-11] Blind management during emergency situations, and unfamiliarity with the laryngeal anatomy or incomplete relaxation of laryngeal muscles during tracheal intubation may be the primary iatrogenic causes. This complication is characterized by hoarseness, breathiness, pain during phonation or swallowing, and choking. Bilateral arytenoid dislocation may result in acute respiratory failure.[7,12-15]

The motion of the cricoarytenoid articulation depends on the articular facet of the cartilage and its

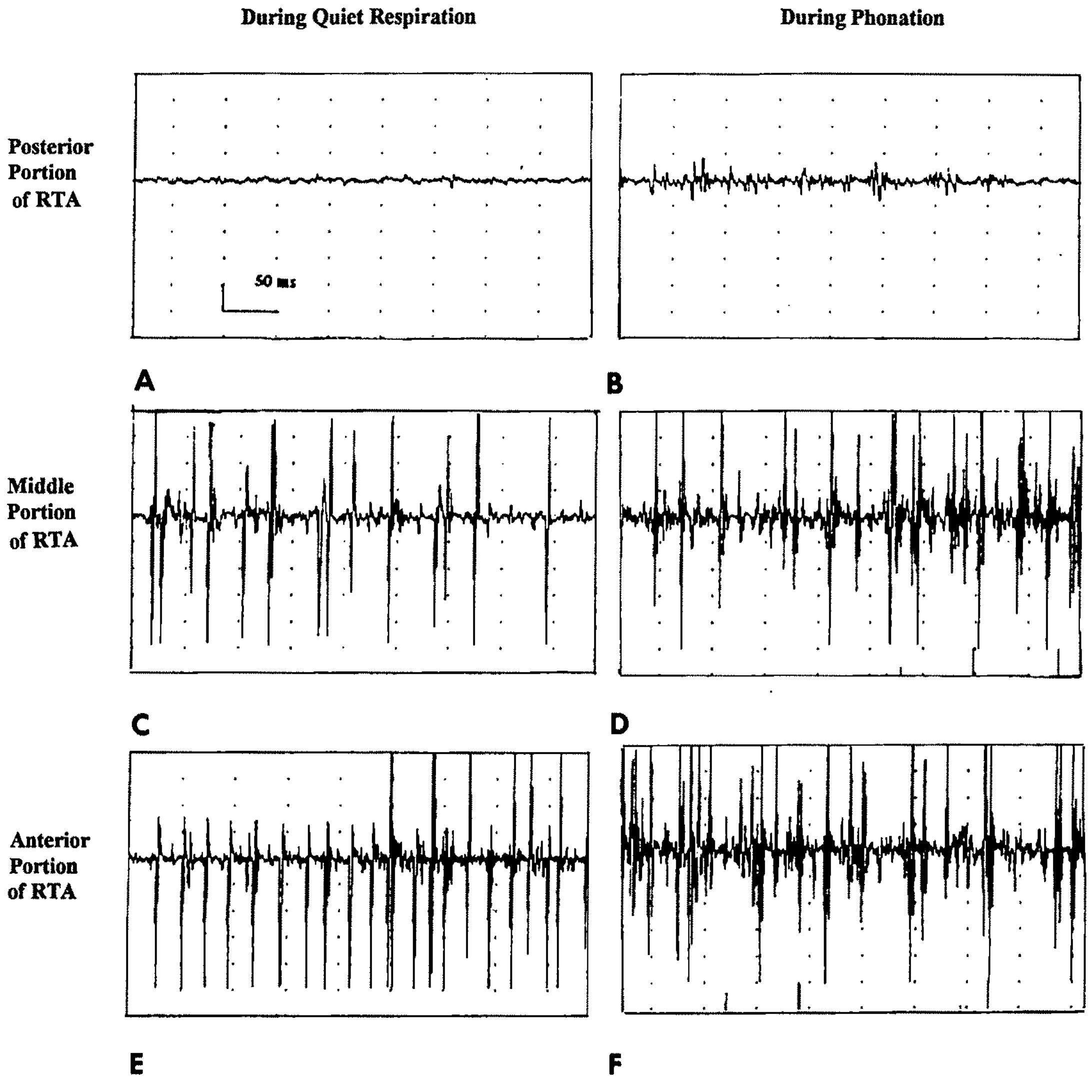
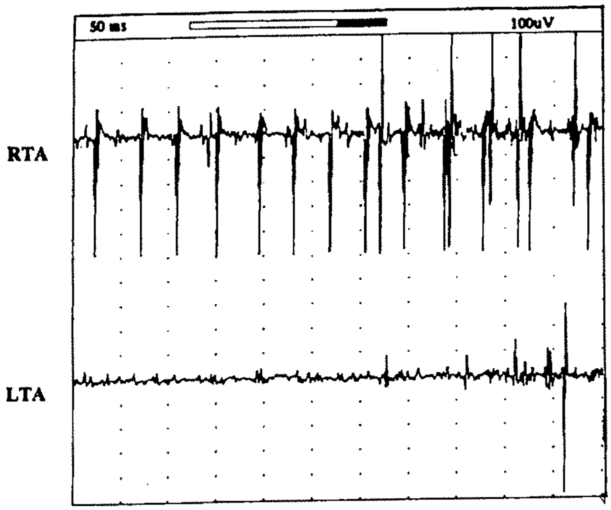


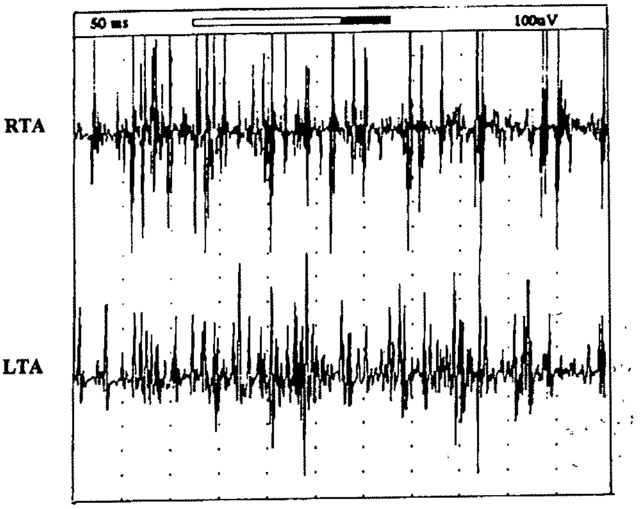
Fig 1. (Case 1) Laryngeal electromyography (EMG) signals recorded from different portions of right thyroarytenoid muscle (RTA). A,B) Posterior portion, C,D) middle portion, and E,F) anterior portion during A,C,E) quiet respiration and B,D,F) phonation. Note that high-frequency discharges occur during quiet respiration, as shown in anterior and middle portions of RTA, suggesting laryngeal myopathy. Recruitment patterns are demonstrated during phonation from anterior and middle portions of RTA, but abnormally low amplitude of EMG is seen in posterior portion, indicating denervation caused by intubation trauma.

attached muscles and ligaments. Videostroboscopy in case 1 revealed that the tip of the arytenoid cartilage tended to be anteroinferior, with slightly lateral displacement. The medial surface of the right arytenoid area was found to have a patch of ulcerative pseudomembrane. These findings strongly indicate displacement of the arytenoid cartilage and injury of the cricothyroid joint. Videostroboscopic images provide not only the vocal cord motion and symmetry of the arytenoids, but also a permanent documentation for comparison of cricothyroid joint mobility before and after operative management.

The value of laryngeal EMG in diagnosis of arytenoid dislocation after intubation has been reemphasized by a recent intensive study.[11] Sataloff et al[11] reported that 12 of 13 patients with arytenoid dislocation who underwent laryngeal EMG revealed normal innervation of the laryngeal muscles. Only 1 patient in their series (n = 26) showed paresis of the recurrent laryngeal nerve associated with partial arytenoid fixation. Actually, it is not necessary, in most circumstances, to test the muscular function by EMG in dislocation or subluxation of the other, larger joints in the body. However, in the case of laryngeal joint dislocation, laryngeal EMG plays an important role in the evaluation of vocal fold immobility and muscle function status. The cricoarytenoid joint is synovial-lined, diarthrodial, and surrounded by a dense, fine and fibrous capsule.[11] In addition, there is a very narrow area between the cricoarytenoid joint and the cricothyroid joint. Once the cricoarytenoid joint is



A During Quiet Respiration



B During Phonation of /ee/

Fig 2. (Case 1) Comparison of laryngeal EMG signals from middle portion of right thyroarytenoid muscle (RTA) and left thyroarytenoid muscle (LTA) recorded simultaneously during A) quiet respiration and B) phonation. Note that RTA reveals high-frequency discharges during respiration, but same recruitment patterns during phonation as LTA.

injured, resultant edema would involve the attached muscle and its innervation by the branch of the recurrent laryngeal nerve. The forms of laryngeal damage after intubation have been reported as true vocal cord ulceration, granuloma, paresis, and subglottic edema,[16] besides laryngeal joint dislocation. Computed tomography may provide, anatomically, evidence of dislocation or subluxation of the laryngeal joints.[8] Cerat et al[17] reported that they were unable to evaluate three of eight cricoarytenoid joints with CT because of insufficient mineralization. Sataloff et al[11] recently reported that false-negative results were found in 5 of 17 CT scans for a diagnosis of cricoarytenoid joint dislocation. Obviously, it is difficult to identify any damage involving the muscles and nerves related to cricoarytenoid joint abnormalities without EMG information.

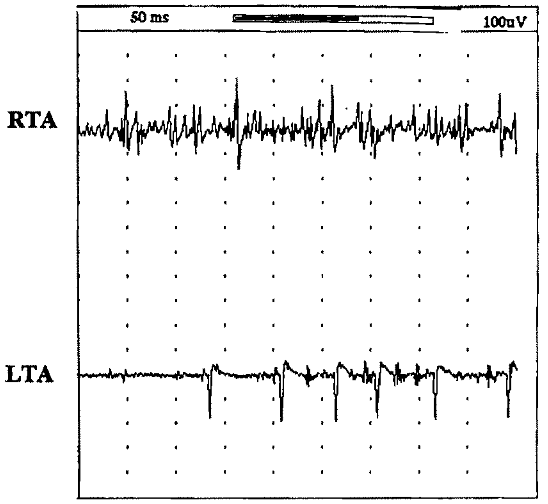


Fig 3. (Case 2) Simultaneous recordings of laryngeal EMG from RTA and LTA during quiet respiration. Polyphasic potentials and positive sharp waves are characteristic in LTA (lower tracing), suggesting denervation and reinnervation. Normal EMG of RTA (upper tracing) is also presented for comparison.

The primary role of laryngeal EMG in differential diagnosis of arytenoid dislocation is to rule out laryngeal paresis or paralysis. Normal patterns of EMG findings provide indirect evidence of dislocation or subluxation of the laryngeal joints without any neurologic complication.[18] Cricoarytenoid joint injuries can be classified into three different patterns based on EMG information. The first pattern, or normal recruitment pattern, of laryngeal EMG is most commonly found in an arytenoid dislocation. Sataloff et al[11] reported that laryngeal EMG in 12 of 13 patients with dislocation of the arytenoid revealed normal innervation to the laryngeal muscles. The second pattern of EMG findings is myopathy. For example, in case 1, laryngeal EMG demonstrated the perturbation of signals in frequency and amplitude, with a firing rate of more than 25/s in the middle and anterior portion of the right thyroarytenoid muscle. These high-frequency discharges are probably due to intubation trauma, and resultant ulcer and inflammation in the right arytenoid area. This pattern of EMG signals is not often found in the laryngeal muscles. Although primary muscle diseases are often seen in neurologic disorders, laryngeal muscular involvement appears to be rare, according to the literature.[19] Abnormal discharges from the laryngeal muscles were only reported in Steinert's disease.[20] The mechanism of high-frequency discharge is unknown. It might be a disturbance of the muscular membrane due to laryngeal joint damage resulting in an impaired relaxation of the muscular fibers. Denervation or reinnervation is the third pattern of laryngeal EMG findings in arytenoid dislocation, shown in case 2. The EMG data of case 2 showed positive sharp waves and polyphasic potentials during spontaneous activity that suggested paresis and reinnervation in the left thyroarytenoid muscle, sampled during quiet respiration (Fig 3). The results suggest that intubation may result not only in damage of laryngeal joints, but also in resultant pathophysiologic changes of the thyroarytenoid muscle and its nerve branches. Previous investigations demonstrated that intubation trauma may cause edema or inflammation of the cricoarytenoid area, and insufficient microcirculation of the larynx.[21] Classification of laryngeal EMG patterns in arytenoid dislocation has clinical significance, since different management strategies would be indicated. In simple arytenoid dislocation with a normal pattern of EMG, immediate reduction of the arytenoid joints should be performed. The dislocation of the arytenoid in patients with myopathy should be monitored and managed with conservative procedures following the resolution of inflammation. Those patients with myopathy who do not have concomitant arytenoid dislocation should be monitored and treated medically until the inflammation has resolved.

Sampling different portions of the laryngeal muscles is also demonstrated to be valuable, as in case 1. After long-term dislocation or subluxation of the laryngeal joints, the thyroarytenoid muscle may be degenerated, and joint ankylosis may occur. In general, the portion of the muscle close to the joint first develops pathologic changes, which gradually spread from proximal to distal. In case 1, the EMG signals showed a high-frequency discharge when the electrode was inserted into the middle and anterior portions, but the discharge was absent in the posterior portion. The absence of recordable EMG responses in the posterior portion of the thyroarytenoid muscle should be interpreted cautiously. Such abnormal EMG findings may be due to recurrent laryngeal nerve neuropathy, but hemorrhage and fibrosis should be ruled out. Clinical follow-up and repeat EMG may clarify the different causes. Submucosal hemorrhage can be found by laryngoscopic and videostroboscopic examinations. Clinical symptoms and EMG findings may return to normal within 4 to 6 weeks if simple hemorrhage exists in the muscle, while a reinnervation and denervation pattern may be observed in those patients with fibrosis or neuropathy in the follow-up EMG. This information provides a dynamic picture of pathophysiology for determining the functional status of the thyroarytenoid muscle.

Early diagnosis with the aid of laryngeal EMG may not only facilitate surgical reduction of the cricoarytenoid joints but also predict the prognosis of vocal fold immobility with higher accuracy. Review of the literature indicates that patients with laryngeal joint dislocation have a better recovery or prognosis if EMG reveals relatively normal patterns in the acute phase in spite of laryngoscopic evidence of vocal fold immobility.[18,22] Complete denervation shown on laryngeal EMG, or a long history of vocal fold immobility with or without the motor unit pattern, generally predicts a poor recovery of glottal movement. After 6 to 8 months of vocal fold immobility, ankylosis of the cricoarytenoid joint is ultimately inevitable. Since closed arytenoid reduction may be impossible in this case, more intensive surgical management is therefore indicated no matter what pattern is shown on laryngeal EMG: denervation or normal. It is suggested that routine laryngeal examination be performed immediately following extubation for every patient, particularly those complaining of hoarseness or choking.

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MORPHOLOGIC AND MOTILITY CHANGES OF NASAL CILIA IN PRIMARY CULTURE CAUSED BY *HAEMOPHILUS INFLUENZAE*

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We focused on the pathogenicity of otitis media with effusion (OME) with respect to the susceptibility of the upper respiratory tract mucosa to *Haemophilus influenzae*. Human nasal polyps in outgrowth culture were used to study *H influenzae* disturbance of the ciliary beat frequency (CBF) and the morphology of cilia. The CBF of control primary culture was 11.7 ± 2.7 Hz. The CBF slowed down significantly, to 8.5 ± 5.7 Hz, after incubation with the filtrate of 10^8 CFU/mL of *H influenzae*, and to 4.1 ± 4.1 Hz with a suspension of 10^8 CFU/mL of *H influenzae* ($p < .05$). In the morphologic study, we classified the shapes of the cilia into five types: normal cilia, immotile cilia, swollen cilia, clumped cilia, and exfoliated ciliated cells. The abnormal shapes of cilia increased after incubation with the suspension or the filtrate of *H influenzae*. By scanning electron microscopy, we saw that aggregated bacteria tended to associate with cilia. Thus, the findings suggest that *H influenzae* disturbs the ciliary clearance of nasal cells and makes them more susceptible to infections.

KEY WORDS — otitis media with effusion, outgrowth culture, stroboscopy.

INTRODUCTION

Many children suffer from acute suppurative otitis media and chronic otitis media with effusion, which are predominantly caused by *Haemophilus influenzae* and *Streptococcus pneumoniae*.[1,2] *Haemophilus influenzae* initiates infection by colonizing on the mucosa, overcoming the mucociliary clearance.[3,4] Some researchers have reported that the suspension[1,5] and the supernatant of *H influenzae*[6,7] have a ciliostatic effect. However, little is known about the morphologic changes of cilia caused by *H influenzae*.

We developed a culture system of nasal cells on coverslips in which cells remained ciliated. This culture system provides a novel approach that will make possible live observations of ciliary beating and the morphology of cilia under stroboscopy. In this study, we focused on the effect of a suspension and a filtrate of *H influenzae* on the ciliary beating and the morphology of cilia.

MATERIALS AND METHODS

Nasal Epithelial Cell Culture. Nasal polyps were obtained from four male patients (35 to 58 years of age) undergoing sinus surgery. We developed a culture system of nasal cells on coverslips. Briefly, freshly obtained nasal polyps were immersed in the transfer medium for 3 hours to inhibit endogenous flora. The medium consisted of Eagle's minimal essential medium, 10% fetal calf serum (FCS), vancomycin hydrochloride (10 µg/mL), amphotericin B (1 µg/mL), gentamicin (40 µg/mL), penicillin G (200 U/mL), and 0.05 mol/L HEPES. We excised the small explants with plenty of cilia from the nasal polyps and seeded them onto the coverslips, which were coated with rat tail collagen in the tissue culture dishes (Corning, Corning, NY). The dishes were filled with Ham's F-12 medium (Gibco Laboratories, Grand Island, NY) supplemented with 10% FCS, insulin 5 µg/mL, transferrin 5 µg/mL, epidermal cell growth factor (Sigma, St Louis, Mo) 10 ng/mL, hydrocortisone 10^{-7} mol/L, vitamin A 90 µg/mL, penicillin G 50 U/mL, and streptomycin 50 µg/mL. The nasal cells were incubated at 35°C in an atmosphere of 5% carbon dioxide and 100% humidity in a sealed tissue culture box (Samplatec, Japan). Five-day cultured cells were used in this study.

Bacteria. Nontypeable *H influenzae* was isolated from the nasopharynx of a patient with otitis media. This organism was stored in 15% glycerol nutrient broth (Difco, Detroit, Mich) at −70°C from a second

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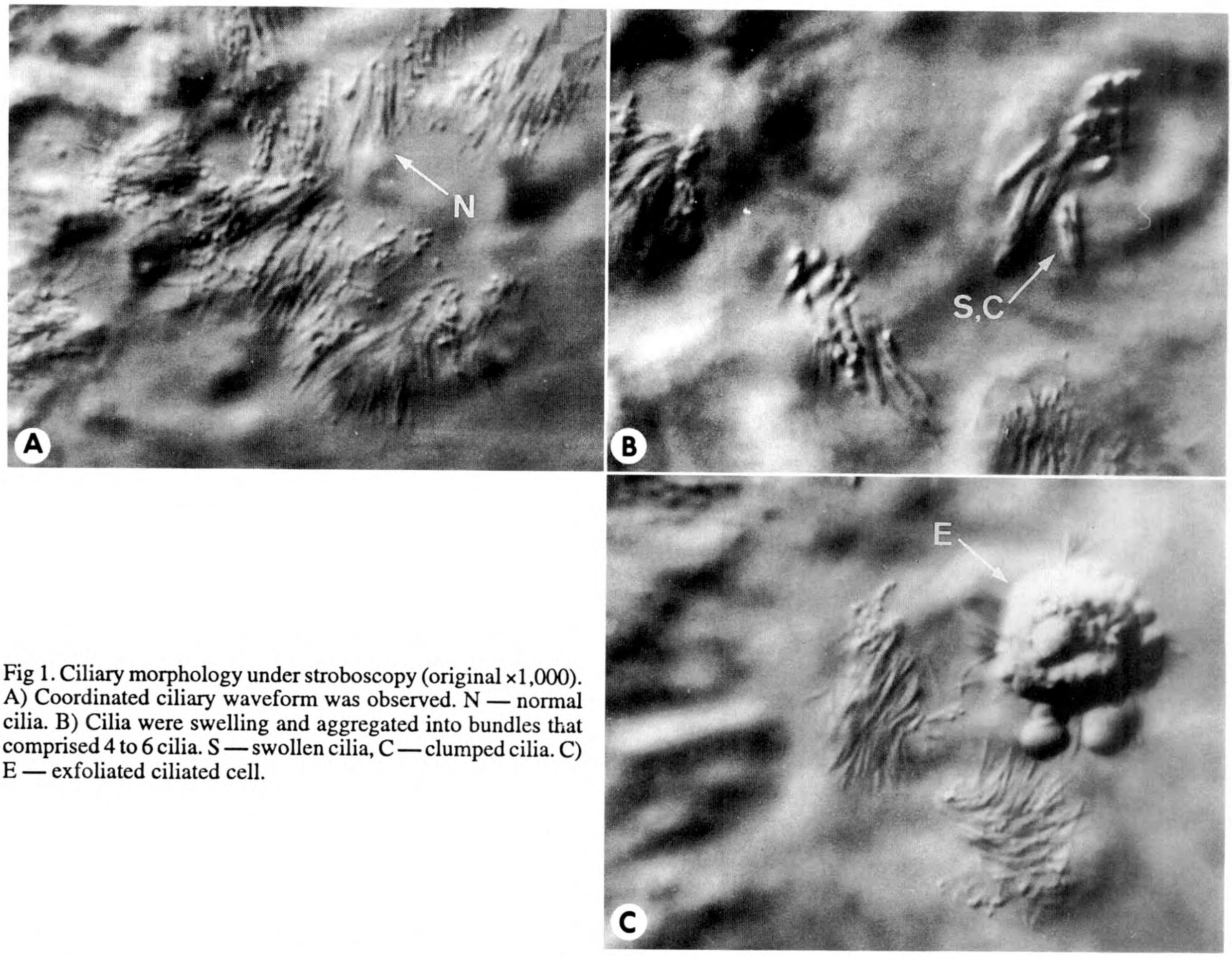

Fig 1. Ciliary morphology under stroboscopy (original ×1,000). A) Coordinated ciliary waveform was observed. N — normal cilia. B) Cilia were swelling and aggregated into bundles that comprised 4 to 6 cilia. S — swollen cilia, C — clumped cilia. C) E — exfoliated ciliated cell.

serial subculture after primary isolation from the patient on a chocolate plate (Becton Dickinson Microbiology System, Cockeysville, Md). Fresh cultures for the experiments below were made by aliquot of the broth passed on the chocolate plate overnight at 37°C. Two colonies of *H influenzae* were inoculated into brain-heart infusion (BHI) broth (Difco) and incubated for 6 hours at 37°C during the logarithmic growth phase. For the negative staining, two colonies were inoculated into BHI broth and incubated overnight at 37°C and resuspended in distilled water. The concentration of bacteria was determined by optical density calibrated against a standard colony count determination.

Negative Staining. A solution of 2% ammonium molybdate–2% ammonium acetate in distilled water was used to negatively stain bacteria. One drop of the bacterial suspension (4.0×10^8/mL) was mixed with two drops of the staining solution. A Formvar-coated copper grid was floated on the surface for 5 minutes.[8] After staining, grids were blotted, allowed to air dry, and viewed immediately by transmission electron microscopy; 100 randomly chosen bacterial cells were scanned and rated for the presence or absence of fimbriae.

Assessment of Ciliary Beat Frequency and Morphologic Study of Cilia. *Haemophilus influenzae* was freshly prepared at the concentration of 10^6 and 10^9 colony-forming units (CFU) per milliliter in BHI broth. The suspensions were diluted into 10^5 and 10^8 CFU/mL with L-15 medium (pH 7.4; Sigma, St Louis, Mo) supplemented with 5 mmol/L N-(2-hydroxyethyl) piperazine-N′-(2-ethanesulfonic acid) (HEPES) and 5 mmol/L N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (BES) (L-15/HEPES/BES). A sterile filtrate of *H influenzae* was prepared by filtration (pore size, 0.2 μm).

After the medium of nasal cells was ascertained to be sterile, the cells were washed three times in the L-15/HEPES/BES. They were then incubated with 1.5 mL of the suspension and the filtrate of each 10^5 and 10^8 CFU/mL of *H influenzae* for 3 hours at 37°C. In the control study, the cells were incubated with 10% BHI broth in 1.5 mL L-15/HEPES/BES. After incubation, to avoid the influence of turbidity of the bacterial suspensions, we washed nonadherent bacteria and the filtrates off the cells three times by L-15/HEPES/BES. We measured 550 ciliated cells for the

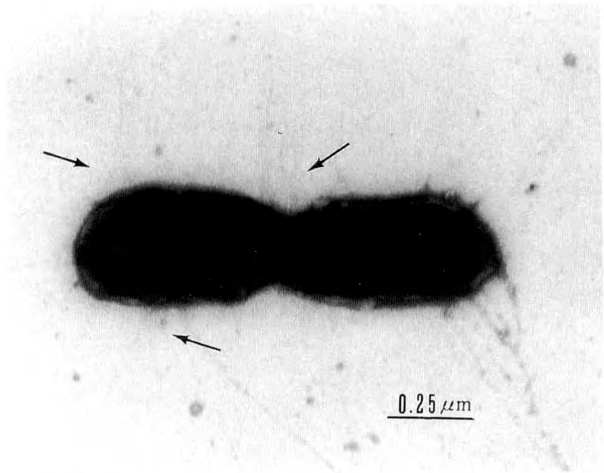

Fig 2. Electron micrograph of *Haemophilus influenzae*, negatively stained with uranyl acetate. Arrows — fimbriae.

ciliary beat frequency (CBF) and 880 ciliated cells for the morphologic study of cilia, using a Zeiss UEM microscope (Carl Zeiss, New York, NY) with a strobe light (model 136, Chadwick Helmuth, El Monte, Calif). We counted CBF at the point at which the ciliary movement synchronized with the strobe light. The output of the stroboscope was analyzed and digitized with a Hewlett-Packard model 5316A reciprocal frequency counter (Hewlett-Packard Co, Wilsonville, Ore). At the same time, the shapes of the cilia were classified by morphologic study into five types: normal cilia (Fig 1A), immotile cilia, swollen cilia, clumped cilia (Fig 1B), and exfoliated ciliated cells (Fig 1C). During the study, we kept the temperature of the cultured cells at 37°C and the pH between 7.0 and 7.4.

Scanning Electron Microscopy. The cultured cells were incubated with 10^8 CFU/mL of *H influenzae* for 6 hours and nonadherent bacteria were washed off. The cells with bacteria were fixed with 2.5% glutaraldehyde in 0.1 mol/L phosphate-buffered saline, and the coverslips were prepared for the examination of scanning electron microscopy.

Statistical Methods. All data were expressed as mean ± SD. The nonparametric Mann-Whitney U test was used in the analysis, and data showing p values of less than .05 were considered significant.

RESULTS

Nasal Epithelial Cell Culture. In the culture system, the outgrowth of epithelial cells consisted of ciliated cells, nonciliated cells, and mucus-producing cells. On the third day of the culture, a confluent outgrowth of cell layers surrounding the explant was observed. In the outgrowth, coordinated ciliary waveforms were observed (Fig 1A). Ciliated cells were observed within 14 days of the culture. Observation on the fifth day revealed that 91.4% ± 6.6% of the ciliated cells were morphologically normal and the CBF was 15.2 ± 4.2 Hz.

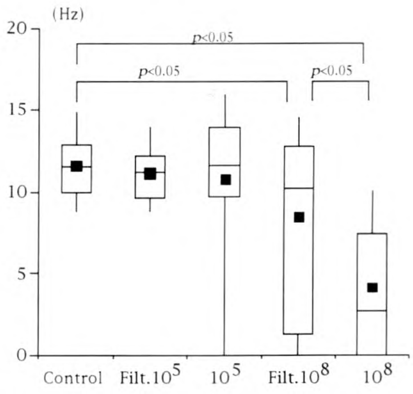

Fig 3. Ciliary beat frequency after incubation with *H influenzae*. Dark square — mean, upper hinge of box — upper interquartile range, middle line of box — median range, lower hinge of box — lower interquartile range, whiskers — from 10% to 90% range, Filt. 10^5 — filtrate of 10^5 CFU/mL *H influenzae*, 10^5 — suspension of 10^5 CFU/mL *H influenzae*, Filt. 10^8 — filtrate of 10^8 CFU/mL *H influenzae*, 10^8 — suspension of 10^8 CFU/mL *H influenzae*.

Negative Staining. Electron micrographs of negatively stained bacteria showed fimbriae in 69%. The fimbriae were approximately 2.5 nm in width (Fig 2).

Ciliary Beat Frequency. The CBF of control primary culture was 11.7 ± 2.7 Hz. The CBF slowed significantly, to 8.5 ± 5.7 Hz, when incubated with the filtrate of 10^8 CFU/mL *H influenzae*, and to 4.1 ± 4.1 Hz with the suspension of 10^8 CFU/mL *H influenzae* ($p < .05$). The suspension of 10^8 CFU/mL *H influenzae* showed a greater cilio-inhibitory effect on the CBF than the filtrate of 10^8 CFU/mL *H influenzae* ($p < .05$). The filtrate of 10^5 CFU/mL *H influenzae* (11.1 ± 2.0 Hz) and the suspension of 10^5 CFU/mL *H influenzae* (10.8 ± 5.0 Hz) did not show a significant effect on the CBF compared to the control (Fig 3).

Morphologic Study of Cilia. Normal cilia were observed in 95.3% of the control cells. When cells were incubated with the filtrate and the suspension of 10^5 and 10^8 CFU/mL *H influenzae*, the number of swollen, clumped, and immotile cilia increased significantly compared to the control (Fig 4). Some ciliated cells showed that their cilia were swelling and aggregated into bundles that comprised 4 to 6 cilia (Fig 1B). These swollen or clumped cilia lost coordinated movement, showing an abnormal dyskinetic, rigid, and planar beating. The CBF of the dyskinetic cells was lower than that of normal cells.

Scanning Electron Microscopy. Bacteria associated to ciliated cells and nonciliated cells in different ways, as observed by scanning electron microscopy,

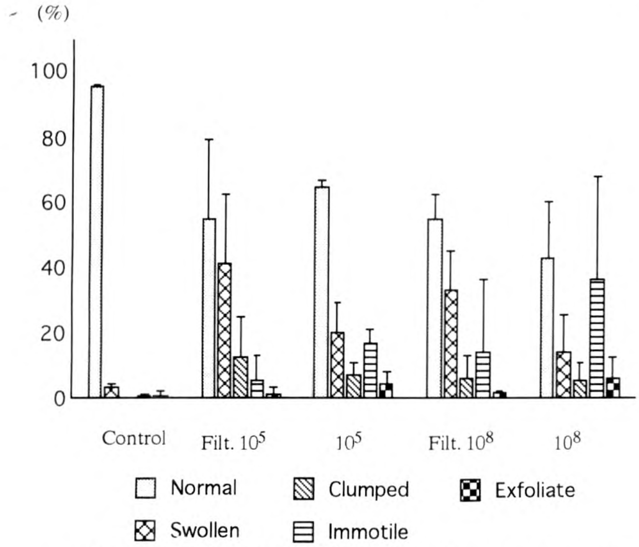

Fig 4. Morphologic findings in cilia after incubation with *H influenzae*. See Fig 3 for abbreviations.

which showed that large aggregates of numerous microorganisms associated to ciliated cells (Fig 5). In higher magnification, the aggregated bacteria associated to the tips of the cilia. On the other hand, single bacteria were observed scattered on nonciliated cells (data not shown).

DISCUSSION

In the present work, the nasal cell culture system showed that ciliated cells were well developed, and coordinated waveforms were observed[9]; these characteristics are important for the study of mucociliary clearance. As the ciliated cells were more scattered in outgrowth culture than in organ culture, we could count CBF and observe the morphology of single cells.

The bacterial concentrations of 10^5 and 10^8 CFU/mL in this study were employed because *H influenzae* is usually found in the range of 10^4 to 10^8 CFU/mL in the nasopharynx and the middle ear cavity of patients with acute otitis media.[6] We used buffers such as HEPES and BES for maintaining the pH of the medium.

The filtrate,[1] supernatant,[2] and lipo-oligosaccharide[10,11] of *H influenzae* were reported to be cilioinhibitory substances. The fact that the filtrate of 10^8 CFU/mL *H influenzae* significantly reduced CBF suggested an inhibitory effect of a soluble substance of *H influenzae* on the ciliary activity. This ciliostatic substance is produced early in the growth cycle of *H influenzae*, and is nondialyzable and heat stable. The substance produced by this strain of *H influenzae* might be an endotoxin.[1] Endotoxin has been found in a large percentage of sterile middle ear effusions.[12,13] Nonviable *H influenzae* or endotoxin purified from this organism has been shown to produce severe inflammatory changes in the middle ear.[14] Ohashi et al[15] reported clumped cilia in guinea pig tubotympanic mucosa incubated with lipopolysaccharide.

Information about the morphologic changes of cilia incubated with bacteria has been scarce in the literature. McDowell et al[16] observed that abnormal cilia such as swollen cilia and clumped cilia were commonly observed in human bronchial epithelium. Neustein et al,[17] Takasaka et al,[18] and Howell et al[19] reported that abnormal cilia were correlated with infections. In our study, we observed abnormal shapes of cilia; ie, swollen, clumped cilia and exfoliated ciliated cells increased and normal cilia decreased after incubation with *H influenzae*. The swollen or clumped cilia lost their coordinated waveform, resulting in an abnormal dyskinetic, rigid, and planar beating. These results suggested that an injurious and

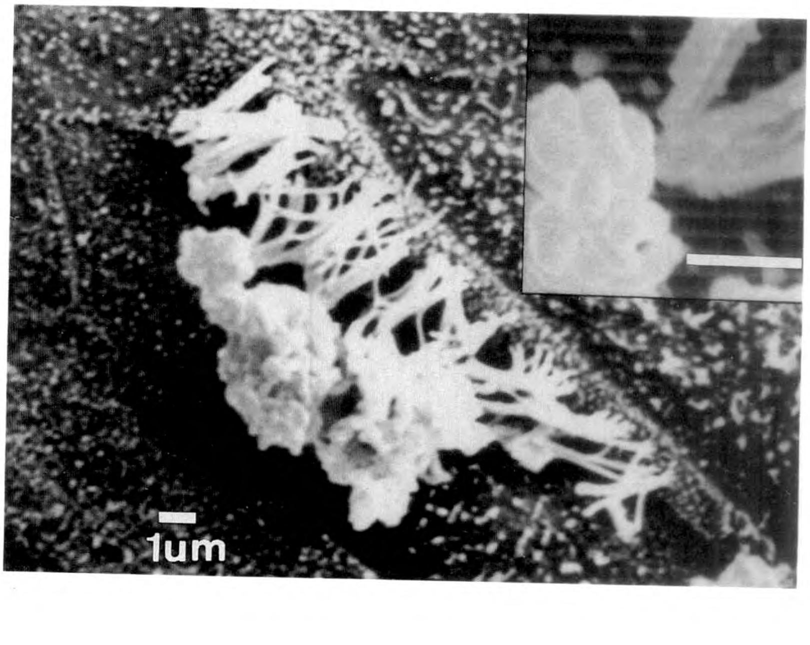

Fig 5. Scanning electron micrograph of cultured nasal cell showing large aggregate of numerous *H influenzae* associated with cilia. Bars — 1 µm. Inset) Aggregated bacteria associated with tip of cilia.

transformative substance may affect cilia in filtrates and suspensions of *H influenzae*. Exfoliated cells increased along with a higher density of *H influenzae*, and the bacteria tended to aggregate to the exfoliated part of the epithelial cells (data not shown).

The mechanisms responsible for bacterial adhesion and cell entry are only partially understood. Recent reports suggest that in vivo, nontypeable *H influenzae* may exist as viable organisms within human adenoid tissue.[20] The substantial adherence of nontypeable *H influenzae* to human conjunctival epithelial cells occurs independently of pili.[21] Recently, a family of high–molecular weight surface-exposed proteins were identified as important in the attachment of nontypeable *H influenzae* to human epithelial cells.[22] The high–molecular weight proteins are morphologically and distributionally different from both *H influenzae* pili and fimbriae.[23,24] In this study, the fimbriation of this strain of *H influenzae* was lost by the serial passages on the chocolate plate, in spite of retention of the hemagglutination (data not shown). However, the fimbriated form of *H influenzae* adhered to epithelial cells more than the nonfimbriated form.[25] In organ culture of adenoid, the adherence was inhibited by the fimbria-specific monoclonal antibody. *Haemophilus influenzae* was observed on columnar epithelial cells and their cilia.[26] Nontypeable *H influenzae* was associated with mucus and with damaged epithelial cells in organ culture of nasal mucosa.[27] A possible role for fimbriae in pathogenesis is still unclear.

In this study, in comparison with the filtrate of *H influenzae*, the bacterial suspension resulted in significantly greater reduction of the CBF. To avoid the possibility that the CBF might be slowed by excessive turbidity of the bacterial suspensions, we washed nonadherent bacteria and the filtrates off the cells three times by L-15/HEPES/BES. However, bacterial aggregation was observed very close to the tips of the cilia under stroboscopy. By scanning electron microscopy, large aggregated bacteria were found to be associated with ciliated cells (Fig 5). Plotkowski et al[28] reported that *Pseudomonas aeruginosa* aggregates trapped the extremities of cilia in primary culture. The association and the local proliferation of *H influenzae* may also reduce the ciliary activity of nasal cells incubated with bacterial suspension.

We showed the morphologic changes of cilia and the slowed ciliary beating after incubation with *H influenzae*. These cilio-inhibitory effects of *H influenzae* could impair the clearance function of nasal cells and facilitate bacterial multiplication, as well as the potential for penetration of the mucociliary barrier following binding with putative receptors on epithelial cells. These findings may explain a major part of the pathogenesis in chronic otitis media caused by *H influenzae*.

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HISTOPATHOLOGIC CHANGES OF THE TYMPANIC MEMBRANE IN ACUTE AND SECRETORY OTITIS MEDIA

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The histopathologic changes observed in 40 normal and inflamed temporal bones of infants and children are reported. The tympanic membranes of patients with acute and secretory otitis media underwent considerable swelling compared to those of normal controls. Tympanic membranes with acute otitis media were thicker than those with secretory otitis media, but the difference was not statistically significant. The epithelial layer showed an increase in the number of cell layers. The lamina propria demonstrated the most significant changes of all layers with a marked swelling due to edema, engorged blood vessels, and inflammatory cell infiltration. Increased numbers of distended capillaries were present, predominantly in the subepithelial connective tissue layer, while infiltration of inflammatory cells was mainly in the submucosal connective tissue layer. By contrast, the involvement of the mucosal layer was modest and was composed of cuboidal cells, except for small islands of metaplastic mucosa with mucus production occasionally encountered in specimens with secretory otitis media.

KEY WORDS — acute otitis media, secretory otitis media, tympanic membrane.

INTRODUCTION

The histologic structure of the tympanic membrane (TM) had been described already in the 19th century as consisting of three layers: external cutaneous, middle fibrous, and inner mucous. The middle fibrous layer was subdivided into an inner circular lamina and an outer radiate lamina.[1-4] Toynbee[5] believed that the TM possessed an additional layer, the "dermis," between the epidermis and the fibrous lamina. Shrapnell[6] was first to describe the pars flaccida of the mammalian TM and found it anatomically different from and more elastic than the pars tensa. Later, it became evident that the pars flaccida is thicker than the pars tensa.[7]

In time, numerous significant contributions were made, and the three layers were distinctly recognized. Lim,[7] Hentzer,[8] and Johnson et al[9] studied the submicroscopic details of the human TM with the aid of the electron microscope. Their work established that the outer epidermal layer is composed of 5 to 10 cell layers of desquamating epithelial cells, thicker at the umbo, at the posterior annulus, and at the anterior annulus than at other locations of the TM. The middle lamina propria of the pars flaccida is different morphologically from that of the pars tensa. The lamina propria of the pars flaccida is formed of loose connective tissue with abundant elastic and collagen fibers, while that of the pars tensa has a more complicated arrangement of layers. It is formed of a subepithelial connective tissue layer, a middle fibrous layer with outer radial and inner circular fibers, and a submucosal connective tissue layer. The innermost layer of the TM is a mucosal layer composed of a single layer of flattened cuboidal cells.

The TM is involved in a variety of middle ear inflammatory conditions, and in many cases clinical diagnosis is based on the appearance of the TM. Nevertheless, the pathology of the TM has received little attention, and only a few reports[10-12] have dealt with certain aspects of these conditions. The present study was undertaken to elaborate on the histopathologic changes of the TM in acute otitis media (AOM) and secretory otitis media (SOM).

MATERIAL AND METHODS

The material consisted of 40 temporal bones removed from infants and children up to 13 years of age at autopsy. They were processed according to a method described elsewhere[13] and serially sectioned into 10-μm-thick sections. The sections were stained with hematoxylin-eosin and periodic acid–Schiff (PAS) stains; light microscopy was employed to study the histopathologic features of the specimens. Twenty temporal bones did not disclose inflammatory changes and were considered therefore normal ones. The remaining 20 temporal bones exhibited various inflammatory changes involving the middle ear mucosal lining. Of the 20 pathologic bones, 9 demonstrated changes compatible with AOM and 11 with SOM. While the former were characterized by

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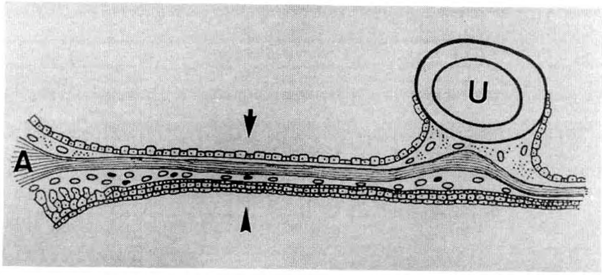

Fig 1. Illustration of tympanic membrane, which is thick at umbo (U), thins out along "drumhead," then thickens again at annulus (A). Arrow — mucosa, arrowhead — epithelium.

MEAN THICKNESS IN MILLIMETERS OF TYMPANIC MEMBRANE AT VARIOUS REGIONS IN NORMAL AND INFLAMED EARS

	Superior	*Umbo*	*Inferior*
Normal	0.062 ± 0.027	0.781 ± 0.121	0.077 ± 0.051
AOM	0.177 ± 0.098	0.946 ± 0.281	0.148 ± 0.064
SOM	0.145 ± 0.057	0.914 ± 0.232	0.128 ± 0.063

AOM — acute otitis media, SOM — secretory otitis media.

polymorphonuclear leukocyte infiltration, the latter were dominated by an increased production of mucus due to mucosal metaplastic changes and mononuclear cell infiltration mostly of lymphocytes and plasma cells.

Measurements were taken at three different sites: 1) at the level of the umbo, defined as the last section that still includes the manubrium, 2) midway between the anterior-superior annulus and the umbo, and 3) midway between the posterior-inferior annulus and the umbo. The following parameters were recorded: 1) the thickness of the TM measured at a magnification of ×100 with a calibrated eyepiece-micrometer, 2) changes in the epithelial layer, 3) the location of the inflammatory cells in the inflamed lamina propria, 4) the site of the distended capillaries in the inflamed lamina propria, and 5) the type of cells in the mucosal layer.

Statistical analysis was performed by a one-way analysis of variance followed by the Bonferroni method of multiple comparison.

RESULTS

Normal Ears. The study reveals that the pars tensa of the TM is composed of three different layers. The outer epithelium consists of three to five cell layers. The middle lamina propria is subdivided into 1) a subepithelial layer composed of loose connective tissue that harbors capillaries and nerves, 2) a middle fibrous layer with outer thicker, radial and inner thinner, circular collagenous fibers, and 3) a submucosal connective tissue layer identical with the subepithelial connective tissue layer but thinner than the former and with fewer blood vessels. The inner mucosa has a single layer of flattened cuboidal cells.

Figure 1 demonstrates that the TM is thick in the region of the umbo, thins out along the "drumhead," and then thickens again at the annulus.

Ears With Otitis Media. The Table shows the total thickness of the TM at various locations in normal ears and in those with AOM and SOM. The measurements clearly indicate that the TM is thicker in inflamed ears compared to inflammation-free ears. It applies to all sites examined and probably to the entire drumhead. Indeed, statistical analysis confirms that TMs with AOM as well as those with SOM are significantly thicker than TMs without otitis media at the superior portion (p = .0001), while the difference between inflamed and normal ears is not significant, either at the umbo or at the inferior portion. Although the TMs with AOM are more swollen than those with SOM, the difference between the two groups of patients is not significant at all measured sites. It should be emphasized that in inflamed specimens, the lamina propria displays more swelling than the other two layers of the TM. Within the lamina propria, the maximal swelling occurs in the subepithelial and submucosal connective tissue layers rather than in the fibrous layer, which remains relatively intact.

Histologic examination of specimens with otitis media discloses many distended capillaries and infiltration of inflammatory cells within the swollen subepithelial and submucosal connective tissue layers of the lamina propria. An increased number of distended capillaries is most conspicuous in the subepithelial connective tissue layer (Fig 2), while the greatest infiltration with inflammatory cells is confined to the submucosal layer (Fig 3).

The epithelial layer of the TM is thicker in patients with both types of otitis media compared to controls, as a result of an almost twofold increase in the number of cell layers.

The mucosal layer, which consists of flat cuboidal cells, does not display metaplastic changes in any of the normal specimens or in those with AOM. Likewise, the mucosal layer of TMs with SOM is composed mainly of cuboidal cells, and in many sections we observed a sharp change from pseudostratified ciliated columnar epithelium, rich in goblet cells, that covers the region near the promontory to a cuboidal mucosa at the annuli. However, small, isolated islands of respiratory epithelium with mucus production were identified in some of the patients with SOM.

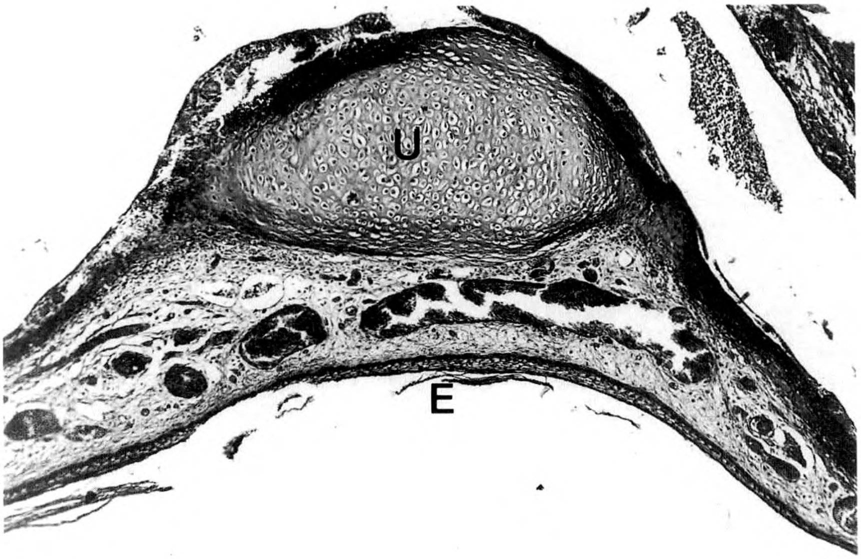

Fig 2. Section at level of umbo (U) shows increased number of distended capillaries in subepithelial connective tissue layer of patient with acute otitis media (H & E, original ×40). E — epithelium.

DISCUSSION

The epithelial layer of the TM in normal ears is thicker in the region of the umbo than in the area midway between the umbo and the anterior and posterior annuli. This finding is in concert with Litton[14] and Naiberg et al[10] and lends support to the hypothesis that the epithelium at the umbo may represent one of the growth centers in the epithelium. Moreover, the epithelium is not the only layer that thickens; similar thickening of the lamina propria also occurs in the region of the umbo, as well as at the anterior and posterior annuli. Consequently, the cross section of the TM is thick in the region of the umbo, thins out more peripherally, and then thickens again at both annuli.

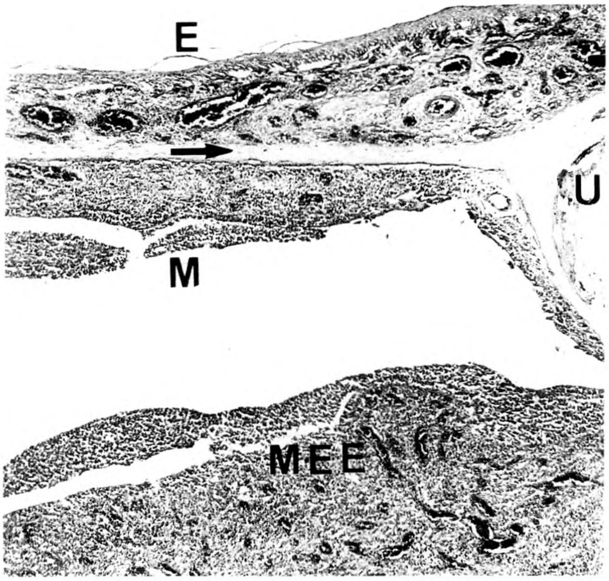

Fig 3. Swollen tympanic membrane of patient with acute otitis media (H & E, original ×40). Proliferation of distended capillaries is present in subepithelial connective tissue layer, while greatest infiltration of inflammatory cells is located in submucosal layer. U — umbo, E — epithelium, M — mucosa, MEE — middle ear exudate, arrow — fibrous layer.

Ruah et al[15] described age-related morphologic changes in the human TM of temporal bones free of otologic disease. It is worthy of note that their measurements of the TM's thickness in the anterosuperior and posteroinferior quadrants, as well as at the umbo, were similar to our results in normal controls.

Although the TM is involved in a variety of middle ear inflammatory conditions and often the clinical diagnosis is based on the appearance of the TM, there are few reports describing histopathologic changes of the TM in otitis media. The present study shows that in AOM and SOM the TM undergoes substantial changes, and each one of its layers participates to some extent in the inflammatory process. Considerable swelling occurs in all sites of the TM in children with AOM and SOM compared to normals, yet statistical significance is present only at the superior portion of the TM. In addition, the study shows that TMs of patients with AOM are thicker than those of patients with SOM, but the difference between the two groups is not statistically significant.

Among the layers of the TM, the involvement of the lamina propria in the inflammatory process exceeds that of the other two layers. Swelling, infiltration with inflammatory cells, and an increased number of distended capillaries affect mostly the subepithelial and submucosal connective tissue layers, whereas the middle fibrous layer remains relatively intact. We reckon that these two layers are composed of loose connective tissue that could potentially become edematous as a result of increased capillary permeability, allowing fluid and cells to escape from the vascular compartment. Yamaguchi et al[16] reported on otitis media with effusion in patients with head and neck tumors and found two patients with proliferation and dilatation of blood vessels in the lamina propria adjacent to the epithelial layer of the pars flaccida. A similar observation is made in the present study, in which proliferation of dilated capillaries is found in the subepithelial and submucosal layers of the lamina propria of the pars tensa in temporal bones with AOM and SOM. Since normal ears contain more capillaries in the subepithelial layer than in the submucosal layer of the TM, engorgement of the capillary bed secondary to inflammation is more prominent in the subepithelial layer. On the other hand, the infiltration of polymorphonuclear leukocytes in AOM and of mononuclear cells in SOM is more prominent in the submucosal connective tissue layer than in the subepithelial layer. This could be attributed to the presence of inflammatory mediators, including chemotactic factors in the exudate[17] that attract leukocytes to the site of inflammation. As a result, these inflammatory cells are found mostly in the submucosal connective tissue layer as they journey from the blood vessels in the subepithelial and submucosal connective tissue layers toward the exudate in the middle ear cavity.

Sano et al[11] recently reported on the histopathologic changes affecting the anteroinferior quadrant of the TM in children with SOM. They observed that the swelling and the inflammatory cell infiltration of the submucosal layer exceeded those of the subepithelial layer. Our findings show that the swelling in both layers is similar — at the anterosuperior quadrant, the posteroinferior quadrant, and the umbo — in children with AOM and SOM. Apparently, the difference between the studies could be ascribed, to some extent, to the fact that we have examined other regions of the TM in patients with SOM as well as with AOM.

The fibrous layer of the lamina propria was found intact in all pathologic specimens, despite the extensive inflammatory changes that involved its neighboring subepithelial and submucosal connective tissue layers. This is at variance with the destruction of the fibrous layer architecture in atelectatic TMs.[12] The latter condition also shows extensive edema and infiltration of the connective tissue with chronic inflammatory cells. It seems that a long-standing negative middle ear pressure is required to induce atrophy and disappearance of the fibrous layer, and probably inflammation per se does not influence its integrity.

Histopathologic changes of the TM in otitis media do not skip the epidermal layer, which thickens in all inflamed temporal bones. Likewise, Naiberg et al[10] reported that in various diseases of the external auditory canal and the middle ear (including AOM and chronic otitis media), the epithelial layer of the pars tensa thickened markedly, in absolute terms and in number of cell layers. This thickening may represent either an increase in mitotic activity or a reduced rate of cell migration.

Hentzer[8] reported that the mucosal layer of TMs with chronic otitis media was pseudostratified, ciliated columnar, with numerous goblet cells. By contrast, our study shows the involvement of the mucosal layer in the inflammatory process to be relatively modest compared to that of the other layers. Metaplastic changes and mucus production are found only in small, circumscribed regions of the mucosal layer of TMs with SOM. This indicates that most of the mucosal layer in otitis media is composed of a single layer of cuboidal cells, while mucus production is rather the exception.

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OTOLARYNGOLOGY UPDATE

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PEDIATRIC SINO-ORBITAL DESMOID FIBROMATOSIS

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Desmoid fibromatosis is a rare tumor of the head and neck. Only five cases involving the sino-orbital region have been previously reported in the literature. In this report we describe the sixth such case, involving a 2-year-old boy, and review the literature.

KEY WORDS — child, fibromatosis, head and neck, sino-orbital region, tumor.

INTRODUCTION

Desmoid fibromatosis is an uncommon tumor in the head and neck and even more rare in the paranasal sinuses. It is characterized as an infiltrative, usually well-differentiated and firm overgrowth of fibrous tissue, locally aggressive, with a propensity to invade and erode bone and soft tissues, putting vital structures in the head and neck region at risk.[1] Desmoid fibromatosis has a high rate of recurrence and mortality. Treatment consists of an adequate three-dimensional imaging evaluation, followed by an en bloc resection with adequate margins. Postoperative radiotherapy, chemotherapy, and, recently, hormonal adjuvant therapy have been used in an effort to control local recurrence.

The occurrence of desmoid fibromatosis in the head and neck is difficult to ascertain because of the classification schemata used by different authors. Ideally, the pathologic diagnosis of the whole group of fibromatoses should be restricted to tumors derived from fibrocytes; however, a number of other cells such as histiocytes, rhabdomyoblasts, synovioblasts, lipoblasts, Schwann cells, and mesothelial cells may act as facultative fibroblasts, and they resemble true fibroblasts so closely that only tissue culture can differentiate them.[2] The classification of these lesions will require a more scientific, objective, and reproducible set of criteria to replace the current diagnosis based on morphology.[3] Using immunohistochemical studies, Fletcher et al[4] have been able to identify a subgroup derived from smooth muscle.

Only five cases of sino-orbital desmoid fibromatosis have been reported in the literature so far, with four of those involving pediatric patients.[5-8] We present a sixth case, originating in a $2^{1}/_{2}$-year-old boy, that involved the left antrum, extending superiorly to the anterior ethmoid air cells, with erosion of the orbital floor.

CASE REPORT

A $2^{1}/_{2}$-year-old boy fell and hit his left cheek a month prior to our evaluation. The mother had become concerned since the child's left cheek had expanded, deforming the left side of the nose. She had also noted that his left eye deviated superiorly, and did not move in tandem with the right eye.

Examination revealed anterior protrusion of the anterior maxillary wall, with bowing out of the left nasal bone and nasal process of the maxilla. The left eye was displaced superiorly, and there was restriction of the inferior rectus muscle movement. The left upper alveolar ridge was displaced inferiorly.

A computed tomography (CT) scan revealed a mass occupying the left antrum, extending to the left anterior ethmoid air cells, with erosion of the left orbital floor. Anteriorly the mass eroded the anterior maxillary wall, which bulged from the mass effect (Fig 1). A magnetic resonance imaging (MRI) scan not only confirmed the CT findings, but better defined the orbital component of the mass.

The mass was excised by a modified partial degloving approach. A trapdoor was made in the anterior maxillary wall and retracted laterally (Fig 2). The mass was then removed in a subperiosteal fashion until the intraorbital component was encountered, at which point it was dissected from the orbital floor periosteum. The defect was reconstructed by using part of the excised bone to repair the anterior maxillary wall and the orbital floor.

The frozen section diagnosis of myxoma was changed to desmoid fibromatosis on permanent section. The slides were then reviewed at M. D. Anderson Hospital and Tumor Institute, where the definitive diagnosis of desmoid fibromatosis was confirmed (Fig 3). Further testing revealed the tumor to be positive for estrogen and progesterone receptors.

On reexploration 3 months later, part of the antrum was filled by adipose tissue originating from the buccal fat pad through a residual bony defect. Fibrous tissue was present from the healing process, but most

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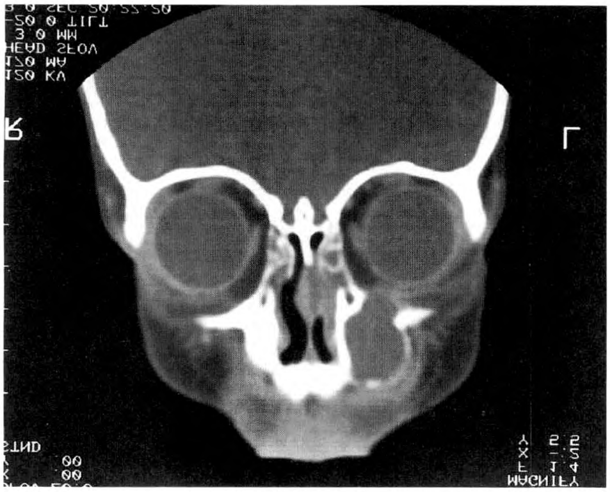

Fig 1. Preoperative coronal computed tomogram depicting expansile lesion extending from left maxillary antrum superiorly to involve orbit.

of the maxillary sinus cavity had reepithelialized. Frank infiltrating tumor was noted along the orbital floor, extending through the periorbita posteriorly. The carbon dioxide (CO_2) laser was then used to vaporize the lesion. The lesion was vaporized from inside out until normal tissue was encountered, and an additional margin of approximately 3 mm of normal tissue was vaporized, including a small amount of the inferior rectus muscle, leaving the majority of the muscle intact. The posterior margin extended to the annulus of Zinn. Additionally, all of the antral epithelial lining was vaporized. The medial wall of the antrum was removed to the degree possible, given the developmental status of the maxillary sinus at this age. The large antrostomy will be used to follow up the child endoscopically in the future.

Adjuvant treatment consisted of a 2-month course of tamoxifen citrate (10 mg twice daily). A post-treatment MRI scan performed 2 years later revealed no evidence of recurrence.

DISCUSSION

One of the most important functions of medical literature is to help guide clinicians in the use of the most up-to-date treatment modalities in order to give optimal treatment to patients. From a clinical point of view, the problem of desmoid fibromatosis is compounded by the fact that the terminology suggests a benign course, whereas in reality these are very aggressive lesions with a high incidence of mortality.

Regardless of the cell of origin, desmoid fibromatoses arise from fibroblasts, many of them have estrogen and/or progesterone receptor sites, and their clinical behavior is similar. In the head and neck they are locally aggressive, with a high rate of recurrence, and because of the proximity to vital structures, frequently lethal.

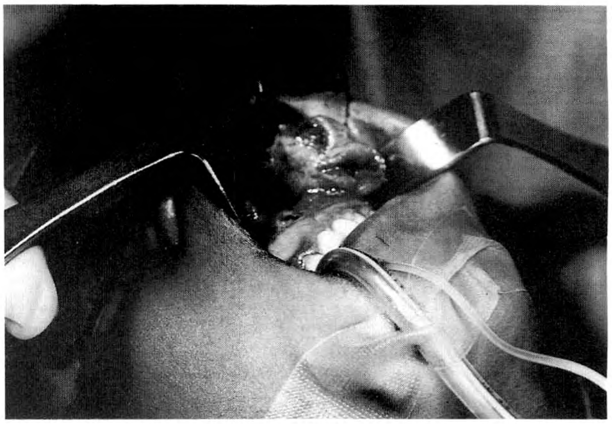

Fig 2. Intraoperative photograph showing lesion and its pseudocapsule, in this case antral periosteum. Capsule was yellowish in color, and contents gray.

In this report we describe our experience in the treatment of this lesion. At surgery, the tumor was noted to have a grayish color and thus was easily differentiated from normal structures. It had a pseudocapsule next to the mucoperiosteum lining of the antrum, which had not been invaded. On the initial excision the pseudocapsule was used as a barrier, and was excised intact with the tumor enclosed within it. At the second operation no tumor was noted to have recurred in this area, and the antrum had relined with mucosa. In the orbit, where the tumor had been dissected from the periorbita, the pseudocapsule was breached and the tumor recurred. The CO_2 laser was invaluable, allowing access to difficult anatomic sites. The extent of gross tumor was easily identifiable from normal tissues because of its gray color. Since the resection extended to millimeters of the optic foramen and its gateway to intracranial contents, further radical surgery was felt to be unwarranted. The medial wall of the antrum was removed for endoscopic follow-up. Adjuvant therapy was undertaken by giving a 2-month course of tamoxifen citrate.

Considering the high rate of recurrence of this tumor and its anatomic site, we felt that adjuvant therapy was necessary. Postoperative radiotherapy has been used, but remains controversial.[9] In 1990 Larson et al[10] reviewed 50 patients that had received radiotherapy to the head and neck. The reported complications, besides the significant risk of developing a second primary, included growth-related disturbances such as hypoplasia of the facial bones, atrophy of the soft tissues, and panhypopituitarism. They also point out that these patients need complex reconstructive surgery during their lifetime, in addition to treatment and monitoring for their hypotha-

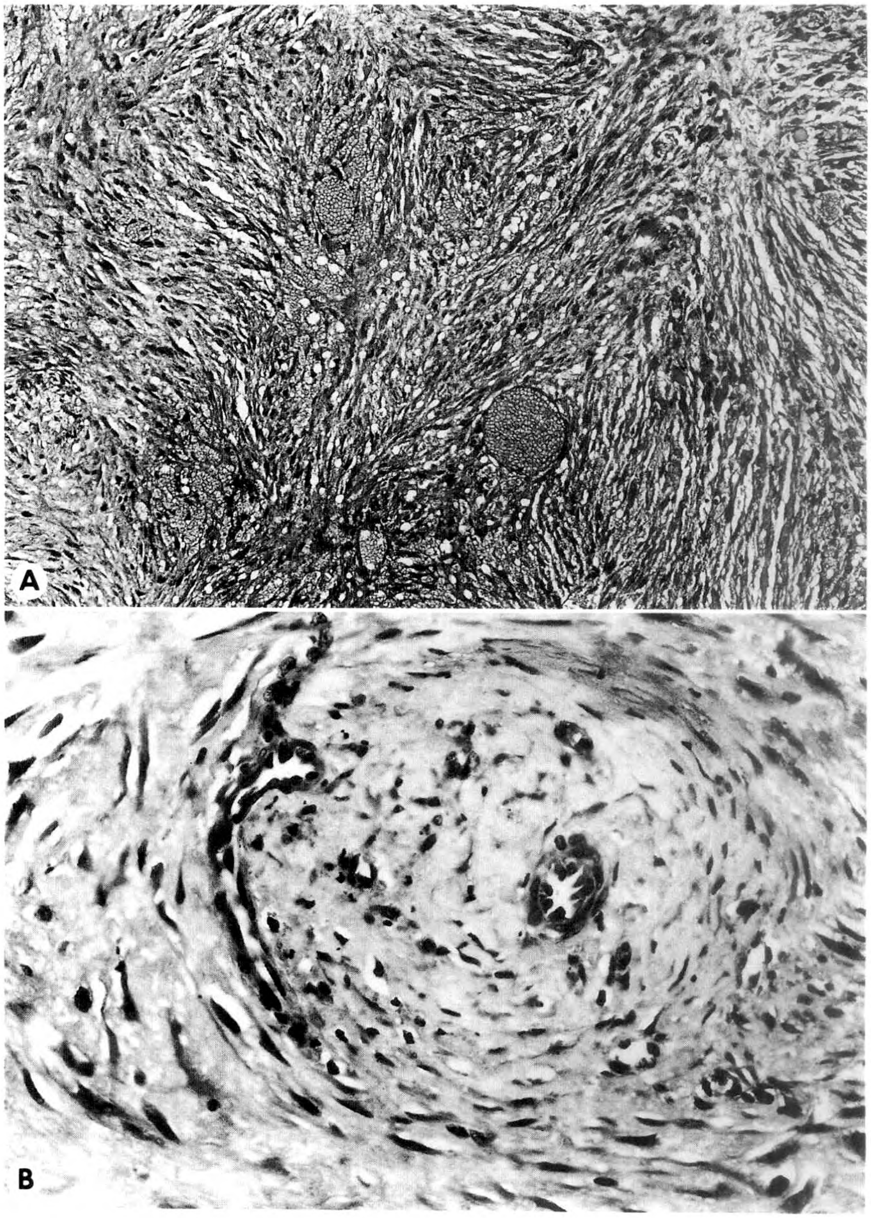

Fig 3. Photomicrographs of excised specimen from maxillary sinus. A) Bundles of fibroblastic cells over fascicular collagenous background are apparent (original ×10). Some thin-walled vessels are also present. B) Two vessels, one in cross section and other elongated (original ×40). Both are compressed by collagenous stroma of fibromatosis.

lamic-pituitary deficiencies.[11]

Chemotherapy has been used with various degrees of success, mostly in abdominal desmoids associated with polyposis.[12,13] In 1982 Goepfert et al[14] reported on the use of chemotherapy in desmoids of the head and neck in a small group of patients with mixed results. Panos and Poth,[15] on the basis of antifibroblastic activity of glucocorticoid hormones, used prednisone for recurrent disease, and Lanari[16] gave progesterone to 11 patients, with 8 responders.

There have been encouraging reports on the use of tamoxifen in the treatment and prevention of recurrent disease.[17] In 1958 Lerner et al[18] published a report describing a number of compounds that inhibited the actions of estrogen. Among these, tamoxifen is the most widely used, and is a nonsteroidal antiestrogen that competitively binds to estrogen binding sites.[13] Additionally, tamoxifen appears to have other mechanisms of action, including an effect on other growth factors. For example, it stimulates the production of transforming growth factor–β, an inhibitory growth factor, as well as inhibiting angiogenesis.[19]

SUMMARY

We have presented the fifth case of desmoid fibromatosis (aggressive juvenile fibromatosis) reported in the literature. The surgical treatment, use of the CO2 laser, and endoscopic follow-up have been described. The actions and use of tamoxifen in presumed microscopic disease in the pediatric population have been explored.

We propose that this disease entity in this anatomic area should be treated aggressively. Surgical treatment remains the mainstay. The use of the CO_2 laser was quite helpful, and the removal of part of the medial wall of the maxilla allowed for easier clinical follow-up. In those fibromatoses that are positive for estrogen and/or progesterone receptors, the use of tamoxifen or one of the newer analogs as adjunctive therapy is indicated. Our experience, as well as that of others, has failed to demonstrate short-term harmful sequelae in the pediatric population. In contradistinction, those lesions that are negative for estrogen and/or progesterone receptors may still respond to tamoxifen. The production of inhibitory factors can, in fact, inhibit not only estrogen-receptor–positive cells, but also estrogen-receptor–negative cells. Tamoxifen's concomitant reduction of angiogenesis decreases the ability of fibrocytes to vascularize and colonize other sites. Those tumors that do not respond, and require adjuvant therapy, may be treated with postoperative radiotherapy or chemotherapy.

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FACIAL CANAL DEHISCENCE: A REPORT OF 1,465 STAPES OPERATIONS

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We retrospectively reviewed 1,465 stapes operations for facial canal dehiscences. The incidence of facial canal dehiscence was found to be 11.4%. A facial canal dehiscence with protrusion of the facial nerve is more common than a dehiscence without protrusion. In addition, 3 cases (0.2%) had a herniation of the facial nerve. Our data suggests that heredity could be one of the factors associated with a facial canal dehiscence. If an operated ear shows a dehiscent facial canal, there is a 29% possibility that the contralateral ear also has a dehiscence. Bilaterality of facial canal dehiscence is, therefore, exceptional.

KEY WORDS — **dehiscence, facial canal, facial nerve, herniation, stapes surgery, surgical finding.**

INTRODUCTION

Anatomic variations of the facial nerve are of significant concern to the otological and neurotological surgeon. Facial canal dehiscence is the most common variation. Since 1894 when Politzer noted that part of the facial canal that traverses the tympanic cavity sometimes presents dehiscence of varying sizes,[1] numerous clinicians and scientists have reported the presence of facial canal dehiscence.[1-8] However, the reported frequency of facial canal dehiscence, which is mainly found in the tympanic segment of the facial canal, varies from 0.5%[3] to 74%[9] of cases, according to different authors. The existing information, on clinically significant dehiscences of the facial canal, is limited. Clinical studies have not been done in adequate numbers, as compared to histologic investigation of up to 1,000 temporal bones.

The cause of facial canal dehiscence is still unclear. The three presumed factors — heredity, inhibitions of proper canal wall formation, and a persistent stapedial artery — that contribute to the formation of a facial canal dehiscence, according to Kaplan,[4] may need to be proved with reliable data.

In this study, we report our observations on facial canal dehiscence based on 1,465 stapes operations. This is the largest number of clinical cases examined to date.

MATERIALS AND METHODS

Medical records of patients treated by stapes surgery at The Fourth People's Hospital of Shanghai in China were retrospectively reviewed for the period from 1962 to 1987. We found 1,465 well-documented surgical records with detailed information about the tympanic segment of the facial canal, which were used for this study.

The 1,465 records related to 1,246 individual patients. The underlying disorder was in all cases otosclerosis. Other diseases were eliminated from this study. Both stapedectomy and stapedotomy were performed. Unilateral operations were performed in 1,027 patients, and bilateral in 219 patients.

Exposure of Facial Canal. The surgical procedures were performed through an ear speculum with the surgical microscope. The skin of the posterior osseous meatal wall was incised beginning just anterior to the short process of the malleus, close to the annulus, and staying lateral at a 6-mm distance from the annulus for most of its U-shaped course. The incision and elevation was carried down to the tympanic sulcus and fibrous annular ligament of the tympanic membrane. The annular ligament was then elevated. The tympanic membrane was folded forward on itself, and then the delicate middle ear mucosa was separated. At this point, occasionally, most of the long process of the incus; the incudostapedial joint; the head, neck, and part of both crura of the stapes; the stapedial tendon; and some of the footplate could be seen. Generally, 2 to 3 mm of the bony rim at the posterior-superior area above the exit of the chorda tympani nerve was removed to expose the stapedial tendon, the footplate, the long process and lenticular process of the incus, the incudostapedial joint, and the stapes superstructure. At this stage, the facial canal was clearly seen just above the niche of the oval window in most cases. If the exposure of the facial canal was insufficient, no further attempts were made to expose the facial canal.

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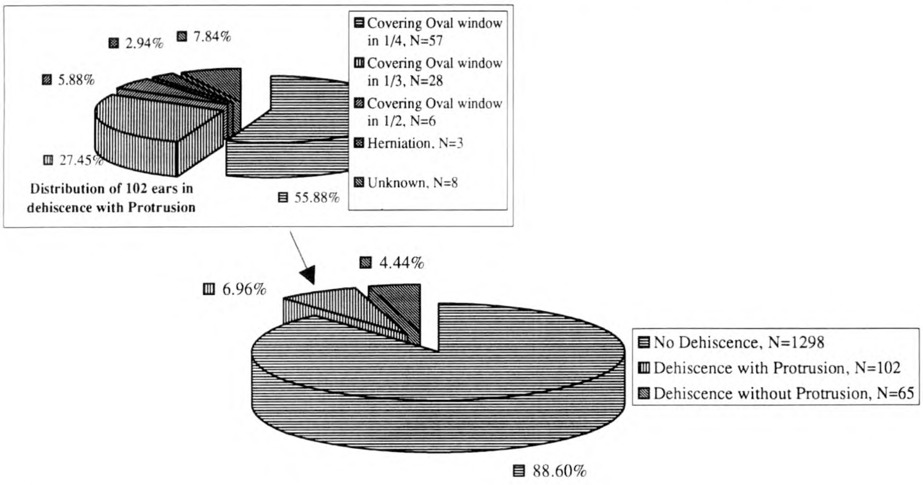

Fig 1. General distribution of 1,465 ears.

Examination of Facial Canal. The exposed facial canal was carefully inspected under high magnification. However, inspection alone, in some cases, was not adequate to confirm the dehiscence. Then, a blunt-tipped instrument was used to help to determine this particular condition. The criteria of facial canal dehiscence, in this study, are of two categories. One entity was dehiscence without protrusion, as evidenced by a lack of continuity of the bony coverage of the facial nerve canal. Another entity was dehiscence with protrusion, in which the nerve came out from its canal to cover the oval window. The findings of an oval window covered by protruded nerve were described as four different grades: one fourth, one third, one half, and herniation. In this study, herniation was defined as a situation in which the prolapsing nerve was completely out of the facial canal and overlaid the whole oval window once the superstructure of the stapes had been removed during the operation.

RESULTS

A facial canal dehiscence was observed in 167 ears (11.4%) of the total of 1,465 stapes operations. Of the 167 ears with facial canal dehiscence, 65 ears had a dehiscence without protrusion, while 102 ears were found to contain a dehiscence with protrusion (Fig 1). In those with protrusion, the nerve came out from its canal to cover the oval window by one fourth in 57 ears, one third in 28, and one half in 6. Three ears had a herniation of the facial nerve. (Eight ears had inadequate descriptions of the nerve's status.)

There were 1,246 patients who underwent stapes surgery. Of these, 152 patients (12%) presented with a facial canal dehiscence. Of the total 1,246 patients, 219 had bilateral and 1,027 had unilateral stapes surgery, respectively. When we looked at the 219 bilaterally operated patients, we found that 41 (19%) had facial canal dehiscences, of which 29 (13%) were unilateral and 12 (5.5%) were bilateral (Fig 2). Of

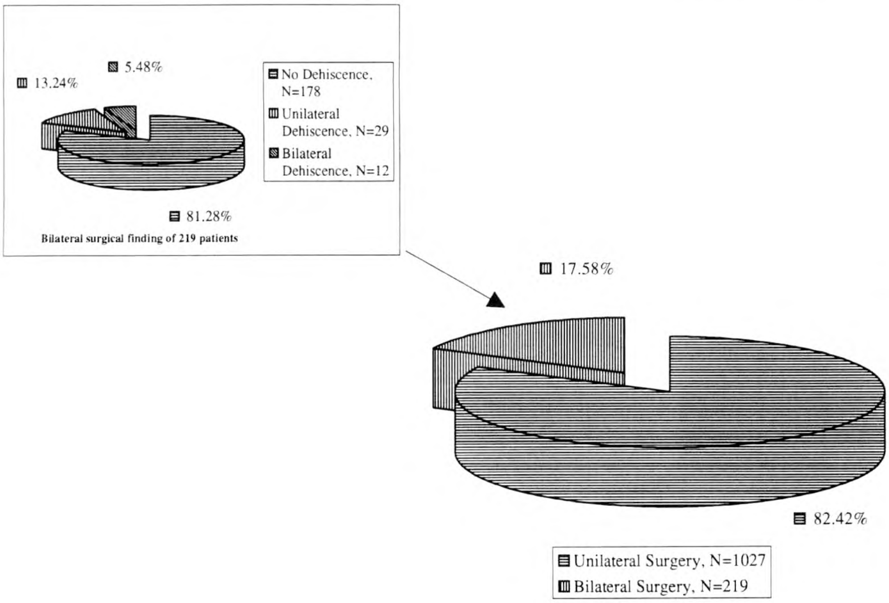

Fig 2. Surgical distribution of 1,246 patients (1,465 ears).

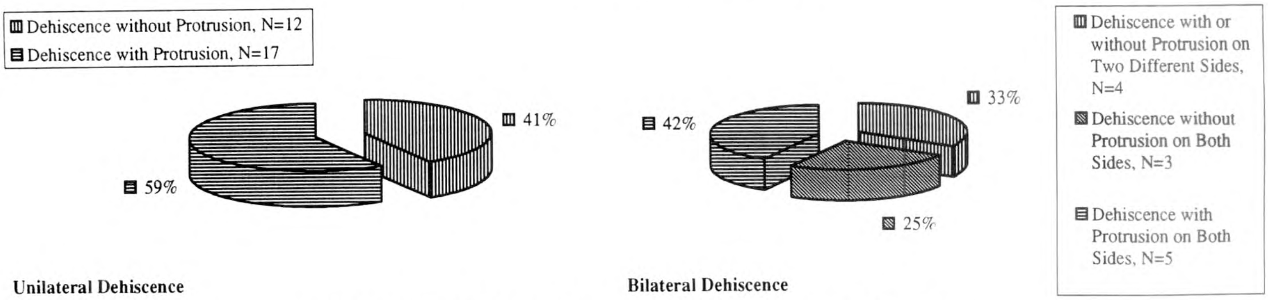

Fig 3. Surgical findings of both unilateral and bilateral dehiscence.

those with a unilateral facial canal dehiscence, 12 patients (41%) had a dehiscence without protrusion, while 17 (59%) had a dehiscence with protrusion. Of those with a bilateral facial canal dehiscence, 4 patients (33%) had a dehiscence with or without protrusion on either side, and 8 patients (67%) demonstrated a dehiscence with or without protrusion in both ears. Figure 3 illustrates more detailed information.

Three cases (0.2%) had a herniation of the facial nerve. In these cases, the prolapsing nerve was completely out of the canal and attached to the stapes. When the superstructure of the stapes was removed at surgery, the nerve was almost overlying the entire oval window.

As shown in Fig 4, out of a total of 41 patients with bilateral surgery, 29 (71%) patients had a unilateral facial canal dehiscence, whereas 12 (29%) patients had a bilateral anomaly.

The most common dehiscence was ovoid in contour with smooth edges.

DISCUSSION

Stapes surgery can provide useful information on the anatomy of the facial canal in the middle ear (see Table[1-6,8-12]). We retrospectively reviewed 1,465 stapes operations to investigate the presence of facial canal dehiscence. To our knowledge, this is the largest series of cases that has ever been studied for this purpose in the world literature. The incidence of facial canal dehiscence was found to be 11.4%.

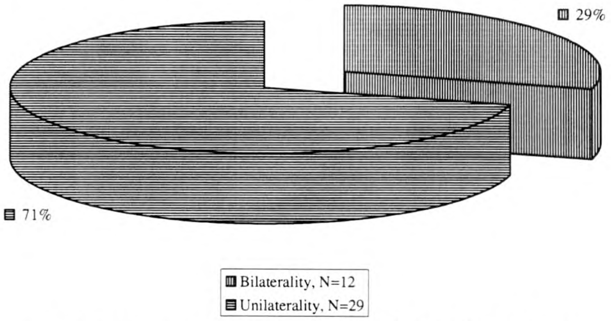

Fig 4. Frequency of unilaterality and bilaterality of facial canal dehiscence in 41 patients with two-sided operations.

Previously reported studies have revealed an incidence of facial canal dehiscence varying from 0.5% to 74% (see Table). It is generally recognized that the incidence of facial canal dehiscence is lower in surgical studies than in histologic studies. As shown in Fig 5, the surgical findings from five different studies[3,4,6,8,10] as well as the present study confirm this difference. There was a mean incidence of 10.7% in reported surgical studies versus 34.7% in six previously reported histologic studies.[1,2,5,9,11,12] A surgical study reveals clinically significant dehiscences of the facial canal, which carry a higher risk of being injured because of protrusion and herniation of the facial nerve. Histologic studies detect microdehiscences of the facial canal,[5] which have no clinical relevance. The finding of the incidence of facial canal dehiscence in the current study is in agreement with the mean incidence value from previous surgical findings — 11.4% and 10.5%.

It is well accepted that a lack of continuity of the bony facial canal is generally situated above the oval window niche (see Table). The dehiscence is usually oval in shape and presents smooth edges.[4] The present study gives findings consistent with those of previous reports. Out of 167 ears with a dehiscent facial canal presented here, 65 (38.9%) had a dehiscence without protrusion. It was, at times, difficult to discern the lack of bony covering of the facial canal with inspection alone, so that gentle palpation with the blunt tip of an instrument was used in all instances. The same experience was reported by Kaplan.[4]

The ratio between dehiscence without protrusion of the facial nerve to dehiscence with protrusion was 65 to 102 in the present study. The higher incidence of facial nerve protrusions in vivo illustrates a disadvantage of postmortem histologic studies.[11] A protrusion covering one fourth to one half of the oval window did not, however, preclude the performance of stapedotomy or stapedectomy in this study.

Three cases (0.2%) had a herniation of the facial nerve in the present study. In these, the protruding facial nerve was in direct contact with the superstruc-

REPORTED STUDIES OF DEHISCENCE OF FACIAL NERVE CANAL

Authors	*Date*	*Source*	*No. of Ears*	*Incidence of Dehiscence*	*Most Common Site of Dehiscence**
Guild[2]	1949	Histologic study	NA	15% (estimate)	Oval window area
Lida (see ref 1)	1951	Histologic study	31	6%	NA
Derlacki et al[3]	1957	Surgical study (SM)	424	0.5%	Oval window area
Cawthorne[6]	1957	Surgical study (MLOW)	31	20%	Oval window area
Hough (see ref 10)	1958	Surgical study (SM)	500	20%-30%	Oval window area
Shambaugh[8]	1959	Surgical study (SM & F)	NA	5%	Oval window area
Kaplan[4]	1960	Surgical study (SM)	100	7%	Oval window area
Beddard and Saunders[11]	1962	Histologic study	52	25%	Oval window area
Baxter[1]	1971	Histologic study	535	55%	Oval window area
Sando et al[12]	1988	Histologic study	100	11.6%	Oval window area
Takahashi and Sando[9]	1992	Histologic study with computer reconstruction	160	74%	Oval window area
Moreano et al[5]	1994	Histologic study	1,000	56%	Oval window area
Present study		Surgical study (S & S)	1,465	11.4%	Oval window area

NA — not available, SM — stapes mobilization, MLOW — membranous labyrinthectomy via oval window, SM & F — stapes mobilization and fenestration, S & S — stapedectomy and stapedotomy.

*Data from surgical studies shown here are available for oval window area only.

ture of the stapes. After removal of the superstructure of the stapes, the prolapsing facial nerve almost covered the whole oval window. In 1 of 3 cases, surgery could not be accomplished, and the 2 remaining patients experienced a limited postoperative hearing improvement. None of the 3 patients had postoperative facial palsy. Herniations of the facial nerve have been repeatedly reported in the literature.[10,13,14] If unrecognized, a herniated facial nerve is at great risk of being injured at surgery.[15] The attempt by an unexperienced surgeon to perform a biopsy on or resect an unidentified "tumorlike" structure within the oval window may have a tragic outcome. We share the words of Mark May, who said, "Don't biopsy a facial nerve in a patient with normal facial function without informed consent — and even with informed consent be prepared to manage the consequences,"[13(p260)] and we would add, "Stop doing surgery at the oval window when you are in doubt about what you are doing."

The pathogenesis of a facial canal dehiscence is unclear. According to Guild,[2] if bilateral symmetry of defects in the bony wall of the facial canal is the rule, rather than the exception, heredity must be regarded as an important etiologic factor.[2] The present study demonstrated the presence of bilaterally symmetric defects in 67% of the patients (25% dehiscences without protrusion and 42% dehiscences with protrusion on both sides, respectively). Our data clearly suggest that heredity could be one of the main factors related to facial canal dehiscence.

Knowledge of embryological development is important in understanding the formation of a facial canal dehiscence. The facial canal is composed of two separate embryological structures: the primordial otic capsule and the Reichert's cartilage originating from the second branchial arch. The facial "ca-

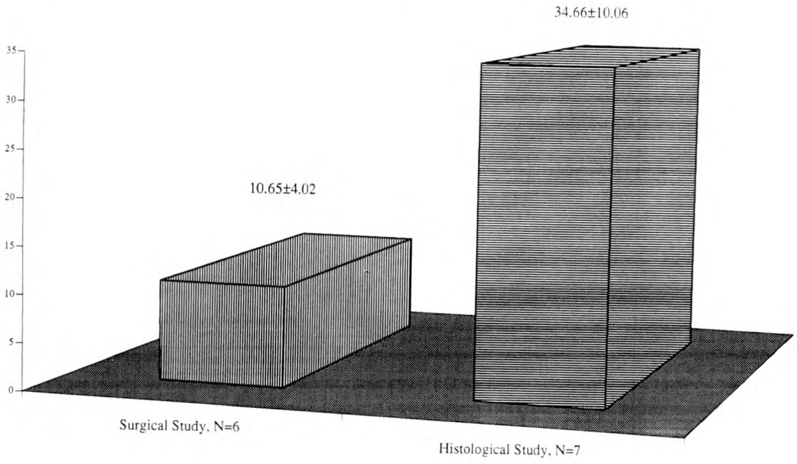

Fig 5. Mean values (incidence of dehiscence) of surgical and histologic findings.

nal" in a 10-week-old fetus is entirely cartilaginous and situated in the canalicular portion of the primordial otic capsule. Reichert's cartilage becomes attached to the otic capsule and forms approximately one quarter of the circumference of the facial canal in the labyrinthine and tympanic segments.[16] The ossification of the canal begins in the fourth month of gestation and is usually complete at the end of the first postnatal year.[17] Most authors believe that the normal development of a closed facial canal is the result of the complete ossification of the cartilaginous canal, and that an incomplete ossification of the bony canal causes a facial dehiscence. However, Declau et al[18] have demonstrated a more complex ossification process of the facial canal. According to Declau et al, the fibrous layers surrounding the facial nerve are also responsible for the final architecture of the facial canal. There is a time sequence for the ossification of these fibrous layers, and its precise molecular mechanisms have an important role in its development.

The frequency of bilateral facial canal dehiscence was 29% in the present study. This is in contrast to the previous finding of 76.3% bilateral incomplete canal closures by Moreano et al.[5] According to our results, bilaterality of facial canal dehiscence is exceptional.

It is important for the surgeon to predict the presence of a contralateral facial canal dehiscence when an operated ear has shown a dehiscence. According to the present study, the probability is 29%.

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REVERSIBILITY OF COMPOUND ACTION POTENTIAL DURING THE ACUTE PHASE AFTER TRANSITORY LOCAL ISCHEMIA

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We investigated the reversibility of compound action potential (CAP) changes induced after transitory local ischemia induced by rose bengal photochemically induced thrombosis of the rat anterior inferior cerebellar artery (AICA). Cochlear blood flow (CBF) was measured with a laser-Doppler flowmeter positioned on the lateral bony wall of the basal turn of the cochlea, and the CAP to an 8-kHz half-wave of sinusoid sound at 100 dB sound pressure level was monitored. The irradiation was started 5 minutes before the rose bengal administration and continued through the thrombosis formation. Tissue-type plasminogen activator (t-PA, 1 mg/kg) dissolved in saline was injected intravenously 2 minutes after complete photothrombotic blockade of the AICA in the rats presenting complete abolition of CAPs just after the vascular occlusions. Nineteen of the 51 rats presented complete abolition of the CAP just after the AICA occlusion, and the thrombosed AICA was successfully reperfused by t-PA administration in 11 of the 19 rats. The result showed that duration of ischemia was the more important determinant for the reversibility of CAPs during the acute phase (p = .00001), and the residual level of cochlear blood flow during ischemia was also an important factor (p = .066). It appeared that the critical time of ischemia for the complete recovery of CAPs was around 5 minutes, and that the critical limit for the irreversibility of CAPs within the acute phase was between 20 and 25 minutes.

KEY WORDS — cochlear ischemia, fibrinolytic reperfusion, functional reversibility, induced vascular thrombosis.

INTRODUCTION

In a previous paper[1] we described an animal model for hearing disturbance caused by inner ear ischemia due to photochemically induced thrombosis with rose bengal (RB) in the central portion of the anterior inferior cerebellar artery (AICA). In this study, we investigated the reversibility of cochlear function during the acute phase after transitory local ischemia with systemic administration of tissue-type plasminogen activator (t-PA) in this model.

MATERIALS AND METHODS

Animal Preparation. Figure 1 shows a schematic illustration of the local anatomy in the present experiment. Fifty-one adult male Wistar rats weighing 240 to 260 g were used. All rats were confirmed to have normal Preyer's reflexes before the experiments. Animals were anesthetized with pentobarbital sodium (50 mg/kg intraperitoneally). A catheter was placed in the femoral vein for drug or RB administration. Another catheter was inserted into the femoral artery and connected to a pressure transducer (Nihon-Kohden, MPU-05, RP-5) for monitoring systemic blood pressure and pulse rate. After tracheotomy, animals were ventilated artificially with a respirator (Harvard 683). Body temperature was maintained at 37°C with a heating pad (American Pharmseal Company, K-module model K-20). The left tympanic bulla and the skull base were then approached ventrally through resection of the larynx, the pharynx, and the longus capitis muscles. Under an operating microscope, bone was drilled away to expose the lateral bony wall of the left cochlea or proximal portion of the ipsilateral AICA without damaging the ossicles or the dura mater. For recording electrocochleograms, an active electrode was placed on the round window membrane and an indifferent electrode was placed in the ipsilateral cervical muscles. A laser-Doppler probe (ALF2100 Advance, Japan; diameter

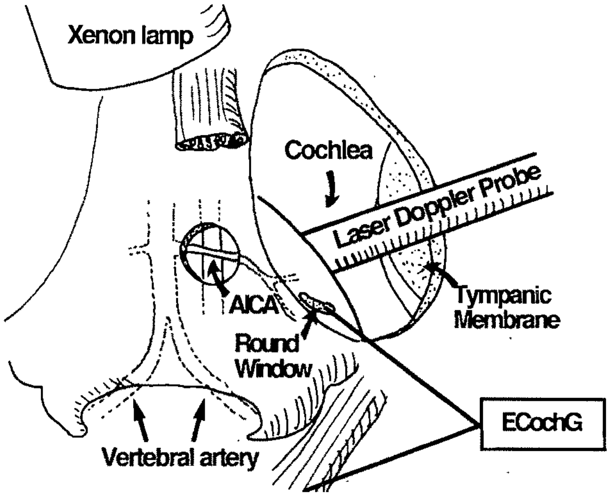

Fig 1. Schematic illustration of local anatomy in present experiment. AICA — anterior inferior cerebellar artery, ECochG — electrocochleography.

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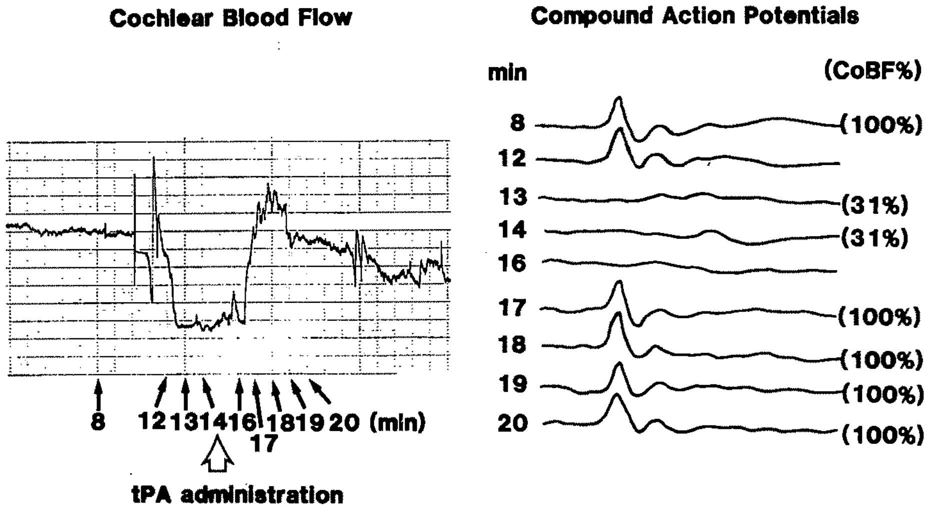

Fig 2. Typical tracing of cochlear blood flow (CoBF) and compound action potentials recorded in rat showing successful reperfusion of thrombosed anterior inferior cerebellar artery following complete abolition of compound action potential. In this example, occlusion period was 4.5 minutes and residual level of CoBF during vascular occlusion was 31% of baseline level. tPA — tissue-type plasminogen activator.

1 mm) was positioned via a micromanipulator on the lateral bony wall of the basal turn of the cochlea after overlying mucosa was removed with cotton pledgets. The compound action potentials (CAPs) to an 8-kHz half-wave of sinusoid sound at 100 dB sound pressure level were averaged 128 times on a signal processor (Nihon-Kohden, ATAC-350, Japan). The sound stimuli produced by an audible signal controller (Dana Japan, DA502-ARM, Japan) were delivered through an earphone using an interstimulus interval of 75 milliseconds and for a duration of 0.2 milliseconds.

Production of AICA Thrombosis. Rose bengal solution (20 mg/kg, Wako, Osaka, Japan) was injected intravenously at the rate of 1 mL/kg per 10 seconds while the AICA segment proximal to the vessel's bifurcation was illuminated selectively with 1-mm-diameter focused green light of approximately 7,500 lux supplied by a 3-mm-diameter convex lens-headed optic fiber, which was connected to a 75-W xenon lamp (L-3306-01A, Hamamatsu Photonics, Hamamatsu, Japan). The illumination was started 5 minutes before the RB administration and continued through the thrombosis formation. This lamp had a heat-absorbing filter and a green filter (containing a 54-nm-wide band centered at 540 nm). The head of the fiber was placed 15 mm away from the surface of the dura mater.

VALUES MEASURED IN RATS SHOWING SUCCESSFUL REPERFUSION OF THROMBOSED AICA AFTER COMPLETE ABOLITION OF COMPOUND ACTION POTENTIAL

Rat No.	*Residual CBF Level (%)*	*Duration of Ischemia (min)*	*Recovery of N1 Amplitude of CAP (%)**
1	9	26	0
2	30	20	18
3	39	36	0
4	39	18	48
5	31	4.5	100
6	12	7	82
7	18	7.5	68
8	24	3	100
9	18	19	11
10	26	3	100
11	3	2	100

AICA — anterior inferior cerebellar artery, CBF — cochlear blood flow, CAP — compound action potential.

*Highest level observed during first 30 minutes after reperfusion.

Experiments With Fibrinolytic Agent. To investigate the functional reversibility of the cochlea after transitory local ischemia, t-PA (1 mg/kg SUN9216; a gift from Suntory, CL, Japan) dissolved in saline was injected intravenously 2 minutes after complete blockade of the AICA in the rats presenting complete abolition of CAPs just after the vascular occlusions. The CAP recordings were repeated at 1-minute intervals during the acute post-ischemic phase (for the following 30 minutes after the reperfusion). The cochlear blood flow (CBF) and systemic blood pressure were recorded continuously on a pen recorder (NEC Sanei, Japan).

Analysis of Results. Multiple regression analysis with stepwise variable selection was used to analyze the significance of the factors contributing to the functional reversibility of the cochlea. The dependent variable of the analysis was the most recovered level (percent) of the CAP N1 amplitude compared with the pre-ischemic value within the acute phase while both the occlusion period (minutes) and the residual level of CBF (percent) were entered into the analysis. The percent level of CBF was calculated, with the value measured after exsangination considered as 0% and the pre-ischemic value regarded as 100%.

RESULTS

Fibrinolysis of AICA Thrombosis. Nineteen of the

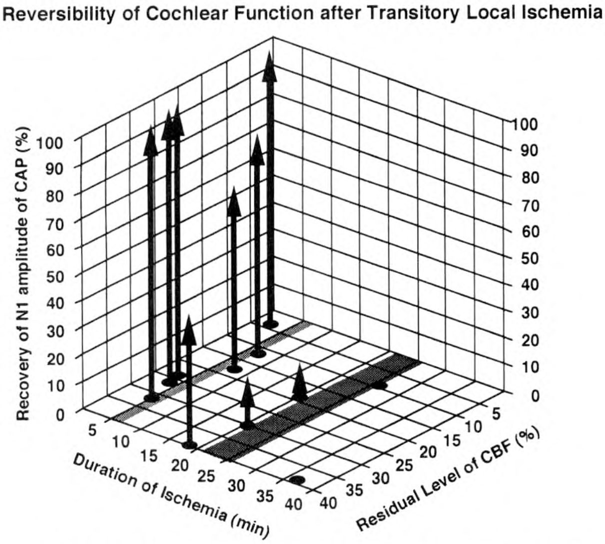

Fig 3. Graphic representation of relationship among three variables. Post-ischemic recovery of compound action potential (CAP) appeared to depend mainly on duration of ischemia. Occlusion period around 5 minutes was upper limit for complete recovery of CAP, and range between 20 and 25 minutes was critical for irreversibility of CAP within acute phase. CBF — cochlear blood flow.

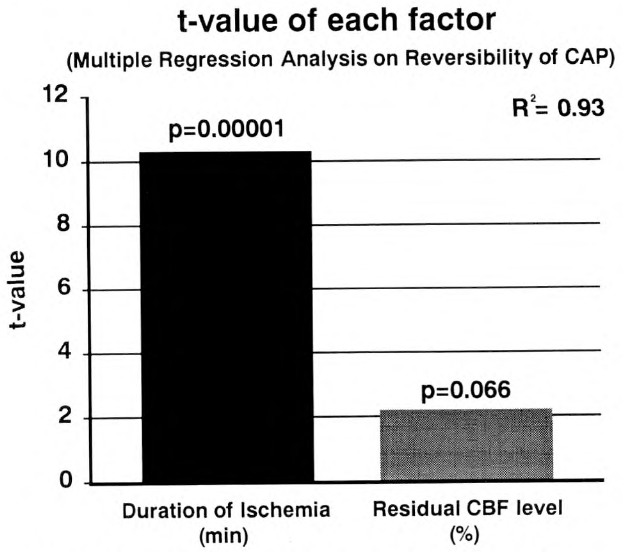

Fig 4. T value of two variables calculated by multiple regression analysis. Coefficient of determination was 0.931. Duration of ischemia was more important determinant for reversibility of compound action potential (CAP), but it is suggested that residual level of cochlear blood flow (CBF) is also important.

51 rats presented complete abolition of the CAP just after the AICA occlusion, and the thrombosed AICA was successfully reperfused by t-PA administration in 11 of the 19 rats. Figure 2 shows the typical tracings of CBF and CAPs recorded in the rats showing successful reopening of the occluded artery. The thrombus gradually grew and finally occluded the AICA, and CBF abruptly decreased to the residual level with a transition time of about 1 minute. The N1 peak of the CAP was abolished just after the photothrombotic occlusion, but immediately recovered to 100% of the pre-anoxic level following reperfusion. In this example, the occlusion period was considered to be 4.5 minutes and the residual CBF level during the ischemic condition was thought to be 31% of the pre-ischemic value.

Post-Ischemic Reversibility of CAPs. The Table shows the residual level of CBF (percent), the duration of AICA occlusion (minutes), and the degree of post-ischemic recovery (percent) of the CAP N1 peak amplitude within the acute phase in the 11 rats. Figure 3 graphically illustrates the relationship of the three variables. Figure 4 shows the *t* value of each two variables in the multiple regression analysis. The regression formula was as follows: [Recovered level of CAP N1 amplitude (%)] = −3.67 × [Duration of AICA occlusion (min)] + 0.801 × [Residual CBF level (%)] + 85.1. Coefficient of determination = 0.931. The analysis demonstrated that the duration of ischemia was the main determinant for the degree of recovery in the N1 peak amplitude during the acute phase after the reperfusion (p = .00001) and that the residual CBF level under the ischemic condition was also an important factor for the functional reversibility of the cochlea (p = .066). It was suggested that the occlusion period around 5 minutes was an upper limit for complete recovery (100%) of the CAP during the acute phase and that the range between 20 and 25 minutes was critical for the irreversibility of the CAPs within the phase.

DISCUSSION

The functional reversibility of the cochlea exposed to temporary local ischemia had been investigated.[2-4] But in these previous studies, the arterial blood supply to the cochlea was completely interrupted and therefore only the temporal factor, duration of ischemia, was discussed as a variable. In this study, we defined the functional recovery, including even the incomplete one from the state of "no response" observed only in the short-term period after reperfusion, as the functional reversibility of the cochlea. We statistically analyzed the contribution of both factors, degree and duration of ischemia, to the reversibility of cochlear function with administration of t-PA in the previously reported animal model.[1] The results demonstrated that the duration of ischemia was the most important determinant for the reversibility of cochlear function during the acute phase after the reperfusion. With regard to the duration of ischemia, it also appeared that the critical time for the complete recovery of cochlear function was around 5 minutes and that the critical range for the functional irreversibility was between 20 and 25 minutes. The residual level of CBF during ischemia was less significant than the duration of ischemia, but it was thought to be an important factor. Perlman et al[2] reported that the cochlear function as reflected in microphonic and action potentials showed complete recovery after vascular occlusion of less than 8 minutes, but showed only partial recovery after obstruction for over 30 minutes. Konishi et al[3] reported that the N1 component of the action potential recovered completely after local anoxic periods of 1 through 16 minutes, but not completely after anoxic periods of 30 to 40 minutes. Kusakari et al[4] reported that the action potentials presented complete recovery after local ischemia of less than 10 minutes and partial recovery after ischemia of 20 to 45 minutes, but no recovery after ischemia of more than 60 minutes. Although the experimental conditions and the species were different from this study, these results seemed to be fairly compatible with ours. We believe that the results of this study can contribute to understanding the pathophysiology of circulatory-induced hearing disturbance. An animal model with higher time resolution enabling long-term experiments and control of both the extent and duration of ischemia may be required for more thorough investigation in the field.

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LANGUAGE DEVELOPMENT IN COCHLEAR IMPLANTED CHILDREN

The International Conference on Language Development in Cochlear Implanted Children will be held December 8-9, 1996, in Lyon, France. For more information, contact Prof A. H. Morgon, Hopital Edouard Herriot, pavillon U, place d'Arsonval, 69003 Lyon, France; telephone (33) 72.11.05.35; fax (33) 72.11.05.34.

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EFFECT OF SC-41930, A POTENT SELECTIVE LEUKOTRIENE B4 RECEPTOR ANTAGONIST, IN THE GUINEA PIG MODEL OF MIDDLE EAR INFLAMMATION

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Arachidonic acid metabolites such as prostaglandins and leukotrienes have been shown to play an important role in the pathogenesis of otitis media (OM). Among these mediators, leukotriene B4 (LTB4) is one of the most potent inducers of inflammatory processes. SC-41930 has been shown to be a specific LTB4 receptor antagonist both in vitro and in vivo. In this study, anti-inflammatory effects of SC-41930 were investigated in a guinea pig model of OM induced by middle ear (ME) inoculation of killed *Staphylococcus aureus*. Outcome of treatment was determined by measurement of myeloperoxidase activity in the samples of ME mucosa, evaluation of temporal bone histopathology, and presence of ME fluids. Myeloperoxidase activity in the SC-41930–treated group was found to be significantly lower than that in the control group. Histopathology of temporal bones indicated decreased inflammation in the treated group as compared to the controls. In addition, ME fluids were absent in four out of six treated animals. These results demonstrate that SC-41930 can produce significant anti-inflammatory effects in this model of OM.

KEY WORDS — animal model of otitis media, leukotriene, SC-41930.

INTRODUCTION

Otitis media (OM) is an inflammatory response of the middle ear (ME) caused by multiple factors such as infection and eustachian tube dysfunction. This inflammatory response begins with cellular infiltration in ME mucosa followed by release of arachidonic acid (AA) from phospholipids of cell membrane by phospholipase. Arachidonic acid is then metabolized by cyclooxygenase into prostaglandins (PGs) and thromboxanes (Txs), and by lipoxygenase into hydroxyeicosatetraenoic acids and leukotrienes (LTs).[1-4]

Leukotriene B4 (LTB4) is one of the most potent inducers of inflammatory processes.[4-7] The proposed effects of LTB4 include chemotaxis of neutrophils and degranulation of lysosomal enzymes, including myeloperoxidase (MPO), collagenase, elastase, and cathepsin G, with the capacity to destroy the connective tissue matrix.[4-7]

SC-41930, a potent selective LTB4 receptor antagonist, was shown to produce significant anti-inflammatory effects in several models of inflammation, including inflammation of the colon, skin, and eye.[8-10] However, the anti-inflammatory role of SC-41930 has not been studied in a model of ME inflammation. In this study, we examined the anti-inflammatory activity of SC-41930 in a guinea pig model of OM induced by ME inoculation of killed *Staphylococcus aureus*.

MATERIALS AND METHODS

Animals. Thirty-two albino guinea pigs (400 to 500 g) obtained from the Research Institute of Animal Diseases, Erzurum, Turkey, with normal MEs as ascertained by otoscopy and tympanometry, were used in this study.

Chemicals. SC-41930 — 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid — was obtained from Searle Research and Development (Skokie, Ill). Hexadecyltrimethyl ammonium bromide and glycine were purchased from Fluka Chemika (Germany). Hydrogen peroxide solution 30% and o-dianisidine (3-3′-dimethoxy benzidine) were purchased from Merck (Germany), and Eastman Organic Chemicals (Rochester, NY), respectively.

Preparation of SC-41930 Solution. Since SC-41930 is insoluble in water, a sodium salt of SC-41930 was prepared by dissolving 1 mol/L SC-41930 in 1 mol/L sodium bicarbonate.

Preparation of Bacterial Suspension. Suspended *S aureus* was killed by sonicator, and the suspension was adjusted to a concentration of 1,100 × 10^6 of *S aureus* per milliliter by use of McFarland Nephelometer Standard 3 in the Department of Microbiology, School of Medicine, Ataturk University, Erzurum,

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From the Departments of Otolaryngology (Sutbeyaz, Karasen, Doner) and Histology and Embryology (Yakan), School of Medicine, and the Division of Biochemistry, Faculty of Science (Ozdemir, Kufrevioglu), Ataturk University, Erzurum, Turkey.

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Turkey.

Immunization of Animals. Three weeks before ME inoculation, all animals were sensitized with a single subcutaneous injection of 0.2 mL of *S aureus* suspension and 0.2 mL of *Bordetella pertussis* (with diphtheria and tetanus toxoids) to stimulate the immune response[11] and enhance the release of LTB4 from neutrophils.[4]

Middle Ear Inoculation of Killed Bacteria. Under anesthesia induced by intraperitoneal ketamine hydrochloride (30 mg/kg), a volume of 0.2 mL of *S aureus* suspension was inoculated into the right ME cavity of all animals through the inferior bulla.

Experimental Groups. The experimental groups were as follows.

Group 1 was the SC-41930 treatment group for MPO assay. Ten animals were injected intraperitoneally with SC-41930 solution (20 mg/kg) 60 minutes before ME inoculation.

Group 2 was the control group for MPO assay. Ten animals were injected intraperitoneally with only sterile saline 60 minutes before ME inoculation.

Group 3 was the SC-41930 treatment group for evaluation of temporal bone histopathology and presence of ME fluids. Six animals were injected intraperitoneally with SC-41930 solution (20 mg/kg) 60 minutes before ME inoculation, and the administration was repeated every 24 hours for 2 consecutive days.

Group 4 was the control group for evaluation of temporal bone histopathology and presence of ME fluids. Six animals were injected intraperitoneally with only sterile saline, in the same manner as in group 3.

Extraction and Assay of MPO Activity in Samples of ME Mucosa. At 24 hours, the animals in groups 1 and 2 were killed painlessly by intracardiac 3% glutaraldehyde injection. The animals were then decapitated, and the temporal bones were removed. The tympanic bulla of the right ear was gently opened, and ME mucosa was removed and stored frozen (–70°C). The MPO activity was assayed as described previously.[12,13] Frozen samples were weighed, minced, and homogenized in phosphate-buffered saline (pH 6.0) containing 0.5% hexadecyltrimethyl ammonium bromide by a Sonic Dismembrator (Fisher Scientific, USA). After homogenization and two freeze-thaw cycles with liquid nitrogen, the homogenates were centrifuged at –4°C, 2,500*g* for 30 minutes by a Heraus Sepatech Santrifuge (Germany). After centrifugation, MPO activity was assayed in the supernatant by incubating 50 μL of diluted sample with 150 μL potassium phosphate buffer (pH 6.0) containing o-dianisidine (0.2 mg/mL) and hydrogen peroxide (0.001%), at 37°C for 15 minutes. The reaction was then terminated by the addition of 100 μL 0.4 mol/L glycine (pH 10). Blank was prepared by the addition of 50 μL distilled water instead of supernatant. The spectrophotometer (LKB-Biochrom, Ultraspec-11 model 4050, Cambridge, England) was adjusted with a blank. The MPO activity was assayed spectrophotometrically by absorbance reading at 450 nm.

ABSORBANCE LEVELS AS INDICATOR OF MYELOPEROXIDASE ACTIVITY IN SC-41930–TREATED ANIMALS AND SALINE CONTROLS

	Absorbance Levels at 450 nm (OD/15 min)	
	SC-41930–Treated Group (n = 10)	*Saline Control Group (n = 10)*
Range	0.205 – 0.302	0.400 – 0.493
Mean ± SD	0.247 ± 0.033*	0.447 ± 0.036
Median	0.243	0.456

OD — optical density.

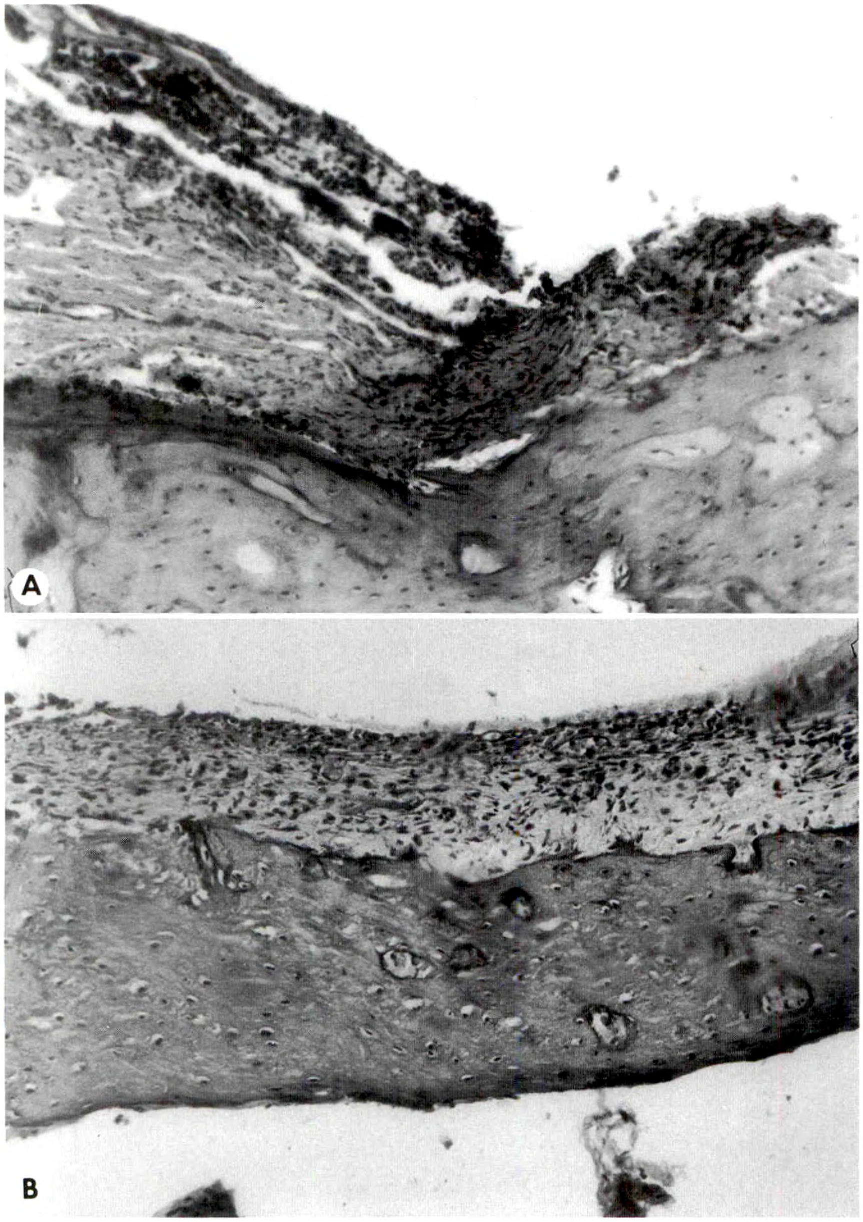
*p < .001 relative to saline control group.

Presence of ME Fluids and Histopathology of Temporal Bone. At 72 hours, tympanometric examination was done before sacrifice. The animals in groups 3 and 4 were then killed painlessly as described above. The temporal bones were removed. The bulla was opened, and the presence of ME fluids was observed. The temporal bones were fixed in phosphate-buffered 3% glutaraldehyde (pH 7.3) for 24 hours, decalcified in 5% ethylenediaminetetraacetic acid for 5 days at 4°C, rinsed three times with the same buffer, dehydrated in graded ethanol, and embedded in paraffin. Each paraffin block was sectioned at 20 μm. Every 10th section was stained with hematoxylin and eosin for microscopic examination. Inflammatory cell infiltration, edema, hemorrhage, and vascularization were noted in the ME mucosa.

Statistical evaluation of data was performed by Student's *t*-test with significance assigned at p < .05.

RESULTS

MPO Activity in SC-41930–Treated and Saline Control Groups. The MPO activities of the SC-41930–treated and control groups are shown in the Table as absorbance values detected spectrophotometrically. The mean ± SD absorbance levels in the saline control group (0.447 ± 0.036) were approximately two times higher than those in the SC-41930–treated group (0.247 ± 0.033). Statistical analysis demonstrated a significant difference between the two groups' absorbance levels (p < .001). Consequently, absorbance levels as an indicator of MPO activity clearly showed that a single injection of SC-



Photomicrographs of guinea pig middle ear mucosa (original ×100). A) Saline control. B) Following treatment with SC-41930.

41930 (20 mg/kg intraperitoneally) significantly reduced neutrophil infiltration at 24 hours, as assessed by the reduction in MPO activity.

Presence of ME Fluids. At 72 hours, ME fluids were present in only two out of six treated animals, but in all saline controls. Before sacrifice, a type B tympanogram as an indicator for the presence of ME fluids was also determined in the animals with ME fluids.

Histopathology of Temporal Bone. In the saline controls, in addition to focal hemorrhage and severe subepithelial infiltration of polymorphonuclear leukocytes (PMNs), the ME mucosa was dramatically thickened with subepithelial edema and dilated capillaries (see Figure, A). In the SC-41930–treated group, however, there was only a mild amount of PMN infiltration in the mildly thickened subepithelial space (see Figure, B), indicating a significant reduction of inflammation.

Inflammation was much less pronounced in the ME mucosa of the SC-41930–treated animals as compared to the controls. In addition, ME fluids were absent in four out of six treated animals, and the MPO activity was significantly lower in the treated group as compared to the control group. These findings with this selective LTB4 receptor antagonist further emphasize the important role played by LTB4 as a mediator of inflammation in OM.

DISCUSSION

Prostaglandins and LTs have been established as important mediators of inflammation.[1-3,14] Prostaglandins and LTs have been determined in ME fluids of chinchillas with experimental OM induced by PGs, LTs, and AA alone and combined with repetitive inoculation into MEs without eustachian tube obstruction and in ME fluids of chinchillas with experimental OM induced by ME inoculation of *Streptococcus pneumoniae* and eustachian tube obstruction, respectively.[1,3]

Leukotriene B4 has become widely viewed as a potent mediator of inflammation and allergy.[5] It is a potent chemotactic and chemokinetic mediator for neutrophils, eosinophils, and monocytes, and is a mediator of lysosomal enzyme release and superoxide generation.[4-6] Leukotriene C4, LTD4, and hydroxyeicosatetraenoic acid do not stimulate any of these PMN functions.[6] Accumulation of PMNs can be quantified by MPO activity.[15] Leukotriene B4 was also shown to have the ability to activate the human neutrophil lipoxygenase by positive feedback on its own synthesis.[5] Brodsky et al[4] reported that LTB4 was found in the highest concentration in the middle ear effusions (MEEs) from 98 human ears, and Nonomura et al[3] showed that the highest-level AA metabolite in experimentally induced chinchilla MEEs was PGE2, followed by 6-keto-PGF1α, LTB4, and LTC4. In the study of MEEs from human and animal models of OM, among the AA metabolites, the levels of LTB4 and PGE2 appeared to represent the degree of acute inflammation, whereas the level of 6-keto-PGF1α appeared to be an index of chronicity of OM.[2]

Several studies suggested that among the metabolites of AA, lipoxygenase products probably play a more significant role than cyclooxygenase products, since treatment with nonsteroidal anti-inflammatory drugs such as ibuprofen seems to worsen the inflammatory changes in the animal models of OM.[2,14,16,17] Jung et al[17] also reported that treatment with ibuprofen in pneumococcal purulent OM in chinchillas causes transformation of the ME mucosa into the secretory type, and this is probably caused by increased lipoxygenase products due to inhibition of cyclooxygenase. Furthermore, it suggested that free use of aspirin in children with acute OM may be one of the important factors in the development of mucoid OM in these children.[2]

More recently, effects of WEB-2086, a potent and specific platelet activating factor (PAF) receptor antagonist, and SCH-37224, an anti-allergic agent that inhibits the formation of LTs and Tx, were tested in an experimental model of OM induced by the ME inoculation of killed *Hemophilus influenzae*, and it was found that treatment with a combination of both inhibitors prevented the development of OM with effusion in all ears better than treatment with each drug alone; this finding indicates the importance of both LTs and PAF in the pathogenesis of OM.[18]

SC-41930 is a selective LTB4 receptor antagonist. It binds to LTB4 receptors on human PMNs, and antagonizes the chemotactic and degranulating activities of LTB4.[19] SC-41930 also binds to f-Met-Leu-Phe (fMLP; a bacterial product) receptors and antagonizes the neutrophil chemotactic and degranulating responses to fMLP and complement 5a (C5a).[19] However, the inhibitory activity of SC-41930 is at least 10 times greater against these PMN functions stimulated by LTB4 than against those stimulated by fMLP or C5a; this finding supports LTB4 receptor selectivity.[7] The anti-inflammatory effect of SC-41930 was also investigated in the animal models of inflammation. Fretland et al[8] tested anti-inflammatory effects of SC-41930 in acetic acid–induced colitis by determining MPO activity and vascular permeability of colonic tissue samples and reported that when given 30 minutes after acetic acid instillation, SC-41930 prevented the rise in MPO and dye extravasation in the inflamed tissue at 4 or 24 hours. Although the peptidoleukotrienes are principally responsible for the increase in vascular permeability during inflammation, SC-41930 has been suggested to correct the vascular leakage indirectly, by reducing PMN infiltration (through LTB4 receptor antagonism) and the subsequent liberation of LTC4, LTD4, and other mediators of enhanced vascular permeability.[8] Middle ear fluids were present in only two out of six treated animals but in all controls. The absence of ME fluids in the majority of the treated animals may be explained by the indirect effect of SC-41930 on vascular leakage. Djuric et al[9] determined the potential dose-related anti-inflammatory activity of SC-41930 by measuring the inhibitory effect of the compound on LTB4-induced neutrophil chemotaxis in the dermis of guinea pigs. The anti-inflammatory activity of SC-41930 was also demonstrated by determining histopathologic and clinical changes at 24 hours in staphylococci-induced ocular inflammation in rabbits.[10]

In addition to the importance of the relationship between the presence of viable bacteria and increased release of LTs in MEEs, AA products, particularly LTs, may be one of the factors in the persistence of MEEs.[4] Therefore, treatment with antibiotics (bacterial killing), as well as with anti-inflammatories that are effective in the lipoxygenase pathway, may reduce the concentration of AA metabolites in MEEs, and may prove to be the most efficacious treatment approach.[4] Furthermore, in the study of bacterial cultures and AA metabolites, LTB4 has been found to be the only metabolite that showed higher levels in culture-positive fluid than in culture-negative fluid.[2] As mentioned above, in addition to being an LTB4 receptor antagonist, SC-41930 inhibits the neutrophil chemotactic and degranulating responses to fMLP and C5a. Thus, a combined use of SC-41930 and antibiotics may have a therapeutic application in OM.

In conclusion, first, our findings confirm the results of others that LTB4 is an important mediator of inflammation in OM, and second, they suggest that LTB4 receptor antagonists such as SC-41930 may be used as effective agents to reduce inflammation in OM.

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SOFTWARE REVIEW

TEMPORAL BONE & POSTERIOR CRANIAL FOSSA. THE HEAD & NECK. VOLUME I-II

Company: Elsevier Science Inc, PO Box 882, New York, NY 10160-0200.

Hardware requirements: CD-I or IBM compatible double speed CD-ROM. IBM compatible, 33 MHz 386 or higher microprocessor; 4 megs of RAM and Microsoft Windows 3.1. Unfortunately, a Macintosh version is not available. Although Soft Windows for the Macintosh will work with Volume I-I, it does not work well with this current release, since the Macintosh's menu bar at the top of the screen pushes several of the program's screen buttons off the bottom of the screen. An oversized monitor is required. The installation is very easy.

This software review is the second in a series that teaches head and neck anatomy through multimedia presentations containing anatomic, histologic, and radiographic pictures of the temporal bone and posterior cranial fossa. As with previous releases, its purpose is to illustrate three-dimensional anatomic relationships.

Volume I-II of the software presents over 10,000 anatomic images in the coronal, sagittal, and axial planes along with "25,000" anatomic names that can be displayed by clicking with a mouse on the displayed structure. These images are photographs of gross anatomic specimens, computed tomography scans, or magnetic resonance imaging (MRI) scans. In the sagittal plane, a histologic image is also available. This software is vastly improved over Volume I-I, the Paranasal Sinus and Anterior Skull Base, and worked flawlessly. It also contains a number of enhancements, including a zoom feature in the CD-I version for viewing cadaveric and histologic images, the ability to specify the degree of enlargement from "Fill Page" to "4×," and the ability to display all four types of images on a single screen. In addition, the speed of location and retrieval of images is enhanced. Unlike Volume I-I, this feature worked flawlessly.

The most useful application of this software is to assist in the instruction and learning of otologic and neurotologic surgery. I found the cadaveric images to be most useful. These images can be displayed in a video mode resulting in a melting away of tissue as one moves through the specimen. This provides an excellent tool in learning anatomic relationships. In addition, one can stop at various points and correlate the cadaveric anatomy with the computed tomography and MRI scan images. As one would expect, the MRI scan added little information about osseous anatomy. The mastoid surgeon will find displaying the images in the sagittal plane from lateral to medial most helpful, since this mimics the standard operative approach. For example, several anatomic sections clearly displayed the relationship between the facial nerve in its vertical course to the middle ear and horizontal semicircular canal. The neurotologist will find viewing images in the axial plane from superior to inferior helpful in learning middle cranial fossa approaches, and in the coronal plane from posterior to anterior in learning posterior fossa anatomy.

Unfortunately, the microscopic resolution of the software's images is poor. The anatomy of the temporal bone is microscopic, and otologic surgery, unlike sinus surgery, is microscopic. The zoom feature enlarges the displayed data, but does not seem to increase resolution, especially in the higher magnifications. The "3×" and "4×" enlargements are very grainy and show pixels; they are of very poor quality and are of little value. The histologic views of the inner ear show no histology. No cells can be identified, nor can any inner ear microscopic structure. The resolution is that of looking at a stained slide with the naked eye. This was a disappointment, since I was hoping for a histologic display of inner ear structures along with anatomic labels.

I would also suggest an enhancement that would allow the displaying of all three planes of view on a single screen, centered around a single point in the middle of the screen. This type of display is now standard in all localization devices being developed for computer-assisted surgical applications (ie, infrared probes developed by Image Guided Technology Inc).

Despite these drawbacks, this software does allow the user to understand many though not all of the important anatomic relationships in otologic and neurotologic surgery. It is a very useful and important addition to the software series being developed by Elsevier.

KEVIN T. KAVANAGH, MS, MD

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EPITHELIAL HYPERPLASTIC LESIONS OF THE LARYNX

The International Conference on Epithelial Hyperplastic Lesions of the Larynx will be held October 28-30, 1996, in Ljubljana, Slovenia. For more information, contact Bostjan Luzar, MD, or Aleksandar Vodovnik, MD, Institute of Pathology, Korytkova 2, 61105 Ljubljana, Slovenia; telephone 386 61 1403042 (Int. 268); fax 386 61 301 816; E-mail Vodovnik@IBMI.MF.UNI-LJ.SI.

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IMAGING CASE STUDY OF THE MONTH
EXTRAMEDULLARY LARYNGEAL PLASMACYTOMA

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ALFRED L. WEBER, MD WILLIAM MONTGOMERY, MD
BOSTON, MASSACHUSETTS

INTRODUCTION

Plasmacytoma is characterized by a proliferation of plasma cells in the bone marrow or, less frequently, in the soft tissue structures. It presents as a solitary lesion or part of a disseminated disease process.[1] Extramedullary plasmacytomas (EMPs) represent fewer than 1% of all head and neck malignancies.[2] Seventy-five to eighty percent of head and neck plasmacytomas occur in the aerodigestive system, such as the paranasal sinuses, nasal cavity (most common), nasopharynx, tonsils, oropharynx, and larynx. Other, uncommon sites include the orbit, salivary glands, skin, and thyroid.[3] Regional adenopathy is encountered in 14% to 26% of cases, but is rarely the first manifestation of EMP.[4] Ninety-five percent of cases occur in patients over the age of 40,[3] with a peak incidence in the seventh decade.

We report this case to illustrate magnetic resonance imaging (MRI) findings that have not been previously described.

CASE REPORT

This 33-year-old woman noticed a change in her singing voice, with progressive worsening in September 1992. An otolaryngological examination (January 1993) revealed a subglottic fullness on the right side. Radiologic examinations were performed following the otolaryngological evaluation. The anteroposterior conventional neck view (Fig 1) showed a homogeneous mass in the right subglottic larynx, extending from the level of the right vocal cords to the inferior margin of the cricoid cartilage. A computed tomography (CT) scan in the axial projection showed the mass to be homogeneous, well defined, and adjacent to the lower right thyroid cartilage and

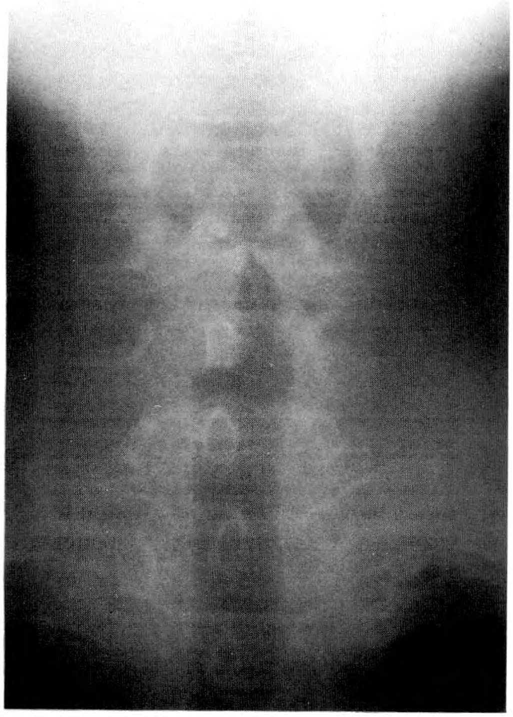

Fig 1. Anteroposterior view with high-kilovolt technique demonstrates subglottic mass on right with slight extension into upper adjacent trachea. Mass obliterates undersurface of right vocal cord.

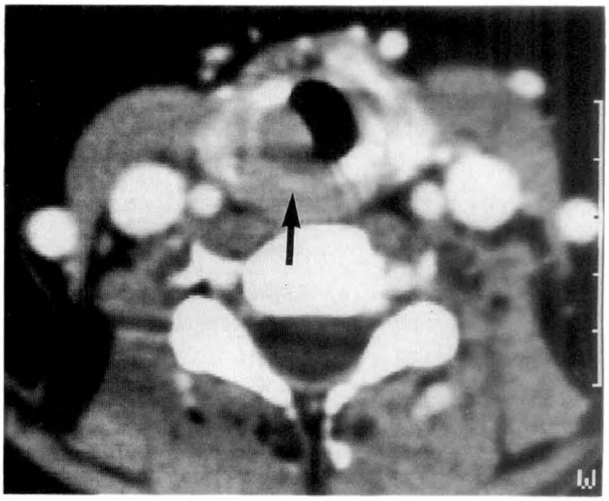

Fig 2. Axial computed tomographic section through larynx at subglottic level demonstrates homogeneous mass, with sharp medial margin in right subglottic area, invading cricoid cartilage posteriorly (arrow).

From the Departments of Radiology (Rodriguez–de–Velasquez, Weber) and Otolaryngology (Montgomery), Massachusetts Eye and Ear Infirmary and Harvard Medical School, Boston, Massachusetts.

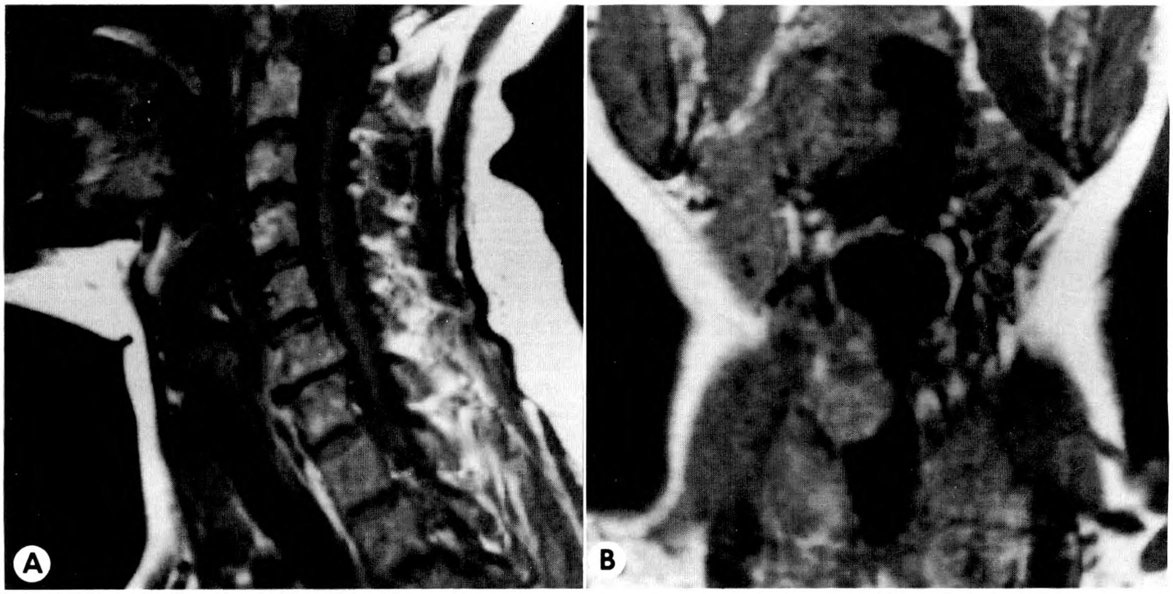

Fig 3. T1-weighted magnetic resonance images through larynx. A) Sagittal, demonstrating low- to intermediate-intensity mass in posterior subglottic space. B) Coronal, demonstrating low- to intermediate-intensity mass in right subglottic space.

adjacent cricoid cartilage with no evidence of calcification. There was a loss and irregularity of the cartilaginous margin adjacent to the mass, consistent with erosion and invasion of the cartilage (Fig 2).

Subsequently, an MRI study, with introduction of gadolinium, was carried out in the sagittal, axial, and coronal projections. The mass was low to intermediate in signal intensity on the T1-weighted images (Fig 3), revealed increased signal intensity on the T2-weighted images, and displayed marked enhancement following the introduction of gadolinium (Fig 4). The tumor was homogeneous, was sharply defined, and invaded the cricoid cartilage (Fig 4A).

DISCUSSION

Plasmacytoma in the larynx is rare, with a total of 82 cases reported up to 1983.[2] Eight additional cases have been published since then.[5-9] It represents about 6% to 18% of all EMPs.[5] These localized lesions in the larynx have been found, in order of frequency, in the epiglottis, vocal cords, ventricles, arytenoids, and subglottic space.[2] Rarely, the tumor extends from the larynx into the mediastinum and causes tracheal compression and displacement.[9] The most common

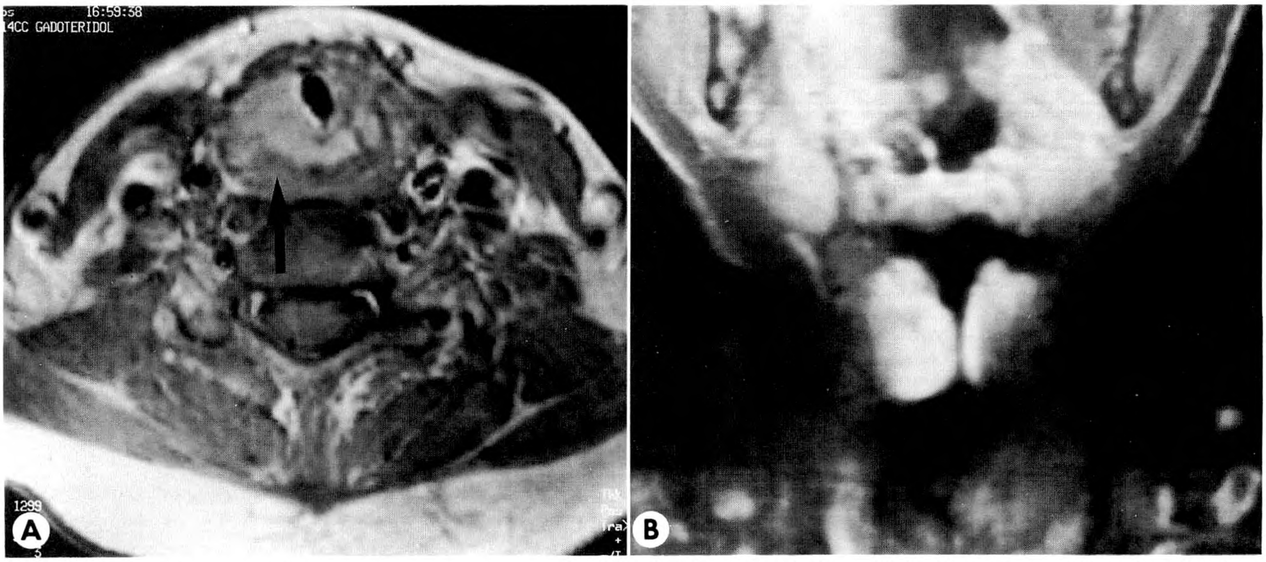

Fig 4. T1-weighted magnetic resonance images taken after introduction of gadolinium. A) Axial, demonstrating well-defined, homogeneous mass with moderate enhancement and cartilaginous invasion (arrow). B) Coronal T1-weighted image with fat suppression technique, demonstrating moderate to marked enhancement of mass.

symptom presented is slowly progressive hoarseness. Dysphagia, stridor, and pain are late symptoms associated with locally aggressive tumors.[5]

Plasmacytoma of the larynx arises in the submucosa and presents as a polypoid, unilateral, smooth, sessile mass with no ulceration. On sectioning, the tumor is usually yellow, brown, or gray in color. On biopsy, plasmacytoma may bleed, since some of these lesions reveal a hypervascular pattern. Histologically, the tumor is composed of sheaths of plasma cells within a sparse and delicate reticular stroma, which may contain amyloid and numerous blood vessels. The plasma cells are of variable sizes and show eccentric, rounded nuclei.[10] The solitary lesion may eventually progress into the disseminated form or into multiple myeloma, which is encountered in 17% to 40% of cases.[1,2] This transition to multiple myeloma, however, remains controversial, and some authors propose that EMP and multiple myeloma represent different entities and not simply part of the spectrum of plasma cell dyscrasias.[1]

On CT, these tumors appear homogeneous, with well-defined margins, and reveal slight to moderate enhancement following the introduction of contrast material. They are usually unilateral and asymmetric within the subglottic larynx. The MRI study reveals low to intermediate signal intensity on T1- and moderate to marked increased signal intensity on T2-weighted images. Following the introduction of gadolinium, there is moderate to marked enhancement. Together, CT and MRI are the method of choice for evaluation of cartilaginous invasion. This is characterized by loss of the cartilaginous cortex and obliteration of the fat in the medullary space. On MRI, the cartilaginous cortex is reflected by low signal intensity, while the medullary fat reveals increased signal intensity on the T1-weighted images. If there is tumor invasion, there is loss of the low-intensity cortex with obliteration of the high-intensity fat by the low-intensity tumor. If the invasion proceeds externally, an extralaryngeal mass will be demonstrated. These tumors contain no calcification, as opposed to chondromas or chondrosarcomas of the larynx. Solitary plasmacytomas have also been reported in the trachea[11] and reveal similar findings as described in the larynx.

In the paranasal sinuses, orbits, nasal cavity, and nasopharynx, plasmacytoma is often bulky and is characterized by a combination of expansion with remodeling of bone and lytic bone destruction. Plasmacytomas rarely may arise in the base of the skull, including the jugular fossa, with lytic bone destruction.[12]

The prognosis is difficult to determine because of insufficient data with long-term follow-up, but appears to be better than the prognosis for multiple myeloma involving the larynx secondarily. The treatment consists of surgical excision, or as an alternative, radiotherapy, since these tumors are radiosensitive.[13]

Other lesions to be considered in the subglottic larynx represent extension of a carcinoma from the vocal cords into the subglottic space. In these instances, the vocal cord usually shows a variable degree of thickening. The extension is usually broad at its base within the vocal cord and tapers inferiorly and laterally along the subglottic wall. In addition, the vocal cord, in these cases, is fixed in a paramedian position. Primary carcinomas within the subglottic space represent fewer than 5% of laryngeal malignancies. These primary subglottic tumors may be squamous cell carcinomas, adenoid cystic carcinomas, or, rarely, adenocarcinomas or mucoepidermoid carcinomas.[14] These malignant tumors in the subglottis may reveal a unilateral or circumferential growth pattern and invade cartilage and the cricothyroid membrane. Benign lesions that show predominance for the subglottic location are chondroma, cavernous hemangioma, and pleomorphic adenoma.[15]

Chondromas frequently arise from the cricoid cartilage and present as a homogeneous, sharply defined, bulky mass. Many of these lesions contain areas of calcification, but a small percentage are homogeneous without calcification.

Other lesions that have been described in the subglottic space represent mesenchymal tumors, and metastases.[16] Their appearance is nonspecific and there are no radiological features that allow a definitive diagnosis. Biopsy is ultimately indicated for the diagnosis and eventual treatment.

The surgical approach of these lesions is by laryngofissure with exposure of the larynx. If the lesion invades the cartilage, a partial or total laryngectomy is mandatory.

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IMAGING CASE STUDY OF THE MONTH

BAZEX'S ACROKERATOSIS PARANEOPLASTICA

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VÉRONIQUE JOUFFRE, MD
LAURENT LACCOURREYE, MD
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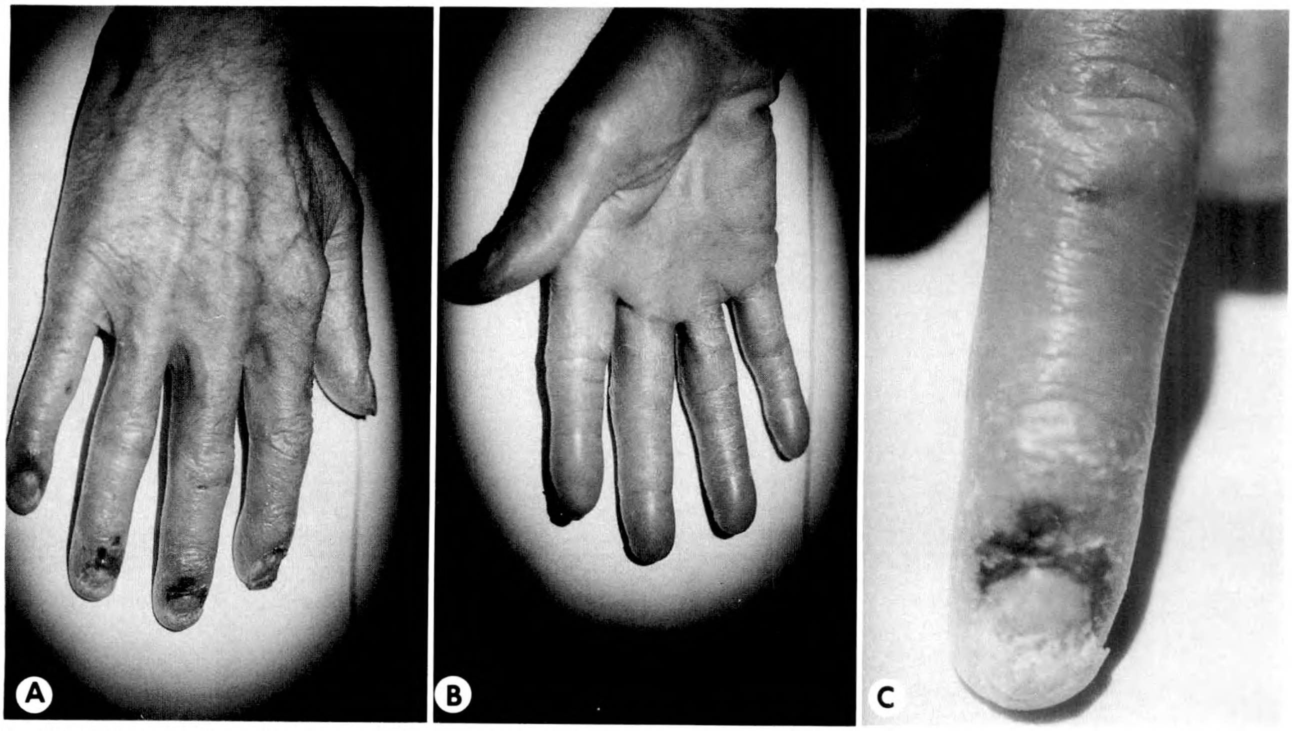
INTRODUCTION

Gougerot and Rupp,[1] in 1922, were the first authors to report a psoriasiform eruption involving the extremities associated with head and neck squamous cell carcinoma. However, it was not until the report of Bazex et al,[2] in 1965, that this dermatosis was regarded as a paraneoplastic process. This condition is one of the rarer cutaneous paraneoplastic syndromes. Fewer than 100 cases have been reported in the literature.[3] A case is presented together with a discussion of the causation and pathogenesis, differential diagnosis, and treatment.

CASE REPORT

A 62-year-old man was referred to our clinic with dysphagia and dysphonia of 3 months' duration. Head and neck examination revealed a tumor located by the left pyriform sinus associated with a 4 × 5-cm ipsilateral subdigastric lymph node. Biopsy of the pyriform sinus revealed a moderately well-differentiated squamous cell carcinoma. The remainder of the findings on head and neck examination were within normal limits. On physical examination, bilateral psoriasiform changes on the fingers (see Figure) and toes were noted. The cutaneous changes did not involve the ears, nose, trunk, palms, or soles. According to the patient, the onset of the cutaneous changes preceded the dysphagia and dysphonia by 6 months. Bacterial and fungal cultures were negative. Results of laboratory studies (hematocrit, serum protein elec-



Bilateral psoriasiform changes on fingers. A,B) Hand shows violaceous psoriasiform erythema and scaling of fingers without involvement of palms. C) Psoriasiform changes and swelling of fingers with periungual acrokeratosis paronychia and thickening of partly destroyed onycholic nail.

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trophoresis) were within normal limits. Skin biopsy was not performed, as the Bazex's syndrome diagnosis is a clinical one and histologic changes in Bazex's syndrome are nonspecific. The pyriform sinus tumor was found to be unresectable. Palliative radiotherapy was performed. Death from distant metastasis occurred by the end of the first posttreatment year, and the primary site was uncontrolled.

DISCUSSION

Bazex's acrokeratosis paraneoplastica (BAP), also termed Bazex's syndrome, is considered a paraneoplastic condition specific to an occult carcinoma. The characteristics of this dermatosis are acral origin, nail dystrophy, cutaneous erythematous squamous plaques with centripetal spreading, and healing only after successful treatment of the tumor. In most cases, as in our report, the associated neoplasia is head and neck squamous cell carcinoma and has metastasized to cervical lymph nodes.[2-5] However, this condition has also been related to squamous cell carcinoma originating from other sites (esophagus, lung) or invading the lymph nodes of the neck without an identifiable primary site.[4,6-8] Furthermore, adenocarcinoma (larynx, prostate, uterus, and gastric), small cell carcinoma (lung, thymus, and vulva), carcinoid tumor (bronchus), anaplastic carcinoma (lung), transitional cell carcinoma (bladder), and myeloma have also been reported in association with BAP.[2-4,7,9,10]

Bazex's acrokeratosis paraneoplastica is a rare paraneoplastic condition. Blanchet et al,[11] in a 10-year follow-up examination of more than 3,000 patients with upper aerodigestive tract carcinoma, noted only 8 patients with BAP. Handfield-Jones et al,[3] in 1992, in a review of the literature noted 86 reported BAP cases. Initially, BAP was identified in middle-aged white men in France.[4] However, reports have been documented in black men and women, and this condition has also been described in patients from Spain, the United Kingdom, Germany, Denmark, Nigeria, Israel, Canada, New Zealand, South America, and the United States.[4,6,8,9,12-19]

According to Bazex and Griffiths,[5] the skin lesions evolve in three clinical stages. Initially, vesicles, scaling, and thickening of the periungual skin, subungual hyperkeratosis, and nail dystrophy associated with minimal ear and nose involvement might be noted. Clinical description of the scales have varied from fine and white to thick and adherent.[7] As the dermatosis progresses, fissure formation and a violaceous color might develop while the skin lesions involve the palms and soles (with a relative sparing of the central portion), the pinna, the bridge of the nose, and adjacent areas of the face.[4,5,7] In later stages the limbs, trunk, knees, elbows, and scalp might be involved.[4,5,7] Rare lesions of the penis and scrotum, and association with lichen planus pigmentosus or acquired ichthyosis, have also been reported.[20-22] The relation between the onset of BAP and the detection of the tumor is variable. In our case the onset of the cutaneous changes on the fingers and toes preceded by 6 months the dysphagia and dysphonia. Bolognia[7] in 1993, in a review of 89 reported cases, noted that BAP preceded the onset of symptoms or diagnosis of the malignancy by an average of 11 months.

Histologic changes in Bazex's syndrome are nonspecific. Hyperkeratosis with parakeratosis, acanthosis, and papillomatosis is usually noted in the epidermis.[4,6,7,19] A perivascular mononuclear infiltrate is noted within the papillary dermis.[4,6,7,19] Vasculitic changes, pigmentary incontinence, and bulla formation have been reported. Results of amino acid analysis of the hyperkeratotic and friable nails were similar to those reported in trichiodystrophy or the BIDS syndrome (brittle hair, intellectual impairment, decreased fertility, and short stature).[23] Immunofluorescence histologic and ultrastructural findings noted a capillaritis with humoral and cellular inflammation.[8,18] Immunoglobulin and complement deposition on the epidermal basement membrane of biopsy specimens from patients with BAP has been reported.[4] According to Bazex et al,[2,5] an allergic or toxic skin reaction to a substance formed by the tumor cells as a causative agent should be regarded as a possible etiopathogenic clue to BAP. Pecora et al[4] suggested a cross-reactivity between antigens found in the tumor and antigens found in the epidermis or basement membrane zone of the skin. An alternative explanation is the secretion by the tumor of autocrine growth factors (transforming growth factor alpha and insulin-like growth factor 1) for human keratinocytes.[7,11]

The differential diagnosis of BAP includes various skin conditions. Involvement of the nose and the ear rules out the diagnosis of primary psoriasis or dermatitis.[7] Concomitant porphyria cutanea tarda, bullous pemphigoid, and epidermolysis bullosa acquisita should be considered in the face of bullae and vesicles.[7] A negative culture rules out fungal and bacterial infection.

Topical keratolytics, corticosteroids, antifungals, and antibiotics were reported to be unsuccessful for treatment of BAP.[7] Improvement with oral retinoids (Tigason) without curative treatment of the underlying neoplasm has been reported.[18] However, only treatment of the neoplasia allowed for disappearance of this condition. Bolognia et al,[24] in a review of 70 reported cases of BAP, noted that in 91% of the patients the cutaneous lesions tended to improve significantly after treatment of the underlying malignancy. Furthermore, relapse of BAP was noted in 83% of cases if the tumor recurred or presented distant metastasis.[24]

Otolaryngologist–head and neck surgeons should be aware of the cutaneous manifestations of BAP, as they provide the clinician a unique opportunity to treat the associated carcinoma at an early, asymptomatic stage and to detect an early recurrence after treatment.

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PATHOLOGY CONSULTATION

DON'T CONFUSE DENTAL SOFT TISSUES WITH ODONTOGENIC TUMORS

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Surgical pathologists are cautioned against the misinterpretation of immature dental tissues (dental papillae and follicles) and dental pulp as odontogenic tumors, especially odontogenic myxomas and fibromas. The close histologic similarity of the immature tissues to tumors may require a clinical-radiologic correlation with the histopathologic specimen in order to distinguish the locally aggressive tumors from innocuous dental tissues.

Because of a general unfamiliarity with the normal developmental structures associated with odontogenesis, surgical pathologists are liable to render diagnoses of odontogenic tumors rather than a proper recognition of these normal structures. Dental papillae, dental follicular tissues, and even pulp of teeth are examples of structures that can mislead the unwary. Ameloblastoma, ameloblastic fibroma, and odontoma can be misdiagnoses, but odontogenic myxoma or fibroma and odontogenic cysts are the lesions most often inappropriately considered.

In the following, we address several of the normal dental developmental tissues and compare them with the odontogenic myxoma and fibroma.

DENTAL PAPILLA, FOLLICLE, AND PULP

Human dentition develops from tooth buds that arise from the embryonic ectoderm of the oral cavity and neural crest cells. The cap consists of three parts: 1) dental organ, from the ectoderm, that produces the tooth enamel, 2) dental papilla, a mesenchymal or ectomesenchymal derivative that forms the tooth pulp and dentin, and 3) dental sac, also from mesenchyme, and the progenitor of cementum and the periodontal ligament.[1]

Under the organizing influence of the proliferating epithelium of the dental organ, the mesenchyme partially enclosed by the invaginated portion of the inner enamel epithelium proliferates and condenses to form the dental papilla, the formative organ of dentin and the primordium of the tooth pulp.[2] The dental papillae show an active budding of a capillary vasculature, and the peripheral cells of the papillae, adjacent to the inner enamel epithelium, enlarge and differentiate into odontoblasts. A well-organized network of vessels appears in the dental papillae by the time dentin formation occurs. Cells of the papillae appear as undifferentiated mesenchymal cells and gradually develop into stellate fibroblasts. With differentiation to odontoblasts of the peripheral cells of the dental papilla, dentin production begins. As this occurs, the papilla is called the pulp organ. The tissue is designated as pulp only after dentin forms around it.[2] This change in developmental nomenclature applies also to the term dental follicle.[2] The enamel organ and, later in the development of teeth, Hertwig's epithelial root sheath are surrounded by the dental sac, consisting of a layer of cells continuous with the dental papilla. The designation dental follicle is suggested for these cells, and the term perifollicular mesenchyme for the cells surrounding the dental follicle.[2] Cells of the follicle give rise to the cementoblasts, the fibroblasts of the periodontal ligament, and the osteoblasts of the developing alveolar bone.[2]

Histopathologic Misinterpretation. The importance of these developmental tissues is in their histomorphologic confusion with gnathic myxomas and other odontogenic tumors. Kim and Ellis[3] have evaluated the frequency of misdiagnosis of the dental follicle, papilla, and pulp in 847 specimens submitted to the Dental Branch at the Armed Forces Institute of Pathology. Only 53.4% of the specimens were correctly identified by the contributing pathologists. Twenty percent were given incorrect diagnoses. The most common incorrect diagnosis was odontogenic cyst, followed by odontogenic myxoma, odontoma, and ameloblastoma. The dental follicle was most often miscalled an odontogenic cyst, whereas the dental papilla was most frequently misinterpreted as

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TABLE 1. SPECIFIED LOCATIONS OF 519 DENTAL FOLLICLES

Tooth Relationship	*Mandible*	*Maxilla*
Third molar	281	149
Canine	5	27
Molar	6	27
Bicuspid	13	3
Incisor	3	5

*Information from 847 cases described by Kim and Ellis.[3]

an odontogenic myxoma. Table 1[3] gives the jaw locations of 495 follicles.

On radiographs, the dental follicle and papilla characteristically appears as a slim, semicircular radiolucency around unerupted or impacted teeth.[3] Larger versions can also be seen in relation to impacted permanent maxillary canine teeth and maxillary or mandibular third molars.[3]

The stromal appearance of the dental papilla, follicle, and pulp is generally one of an increasing fibrosis and decreasing myxoid quality (Fig 1A,B). The follicle also shows variable amounts of lining epithelium, epithelial cell nests, and calcification that are age-related (Fig 1C,D). Between 70% and 45% of follicles will have a demonstrable lining epithelium (columnar enamel, cuboidal, squamous, or, rarely, respiratory-type).[3] Enamel epithelium is the main type found in subjects under 26 years of age, whereas squamous epithelium is seen most often in older patients.[3] The frequency and number of odontogenic epithelial rests in dental follicles also decrease with increasing age of the patients. Kim and Ellis[3] record a 79% occurrence of scattered epithelial rests in follicles. Calcification is seen in about one third of follicles. Myxoid areas in dental follicles are independent of patients' age and have been found in 36% to 73% of follicles.[3] It is the myxoid component that misleads to a diagnosis of odontogenic myxoma or fibromyxoma.

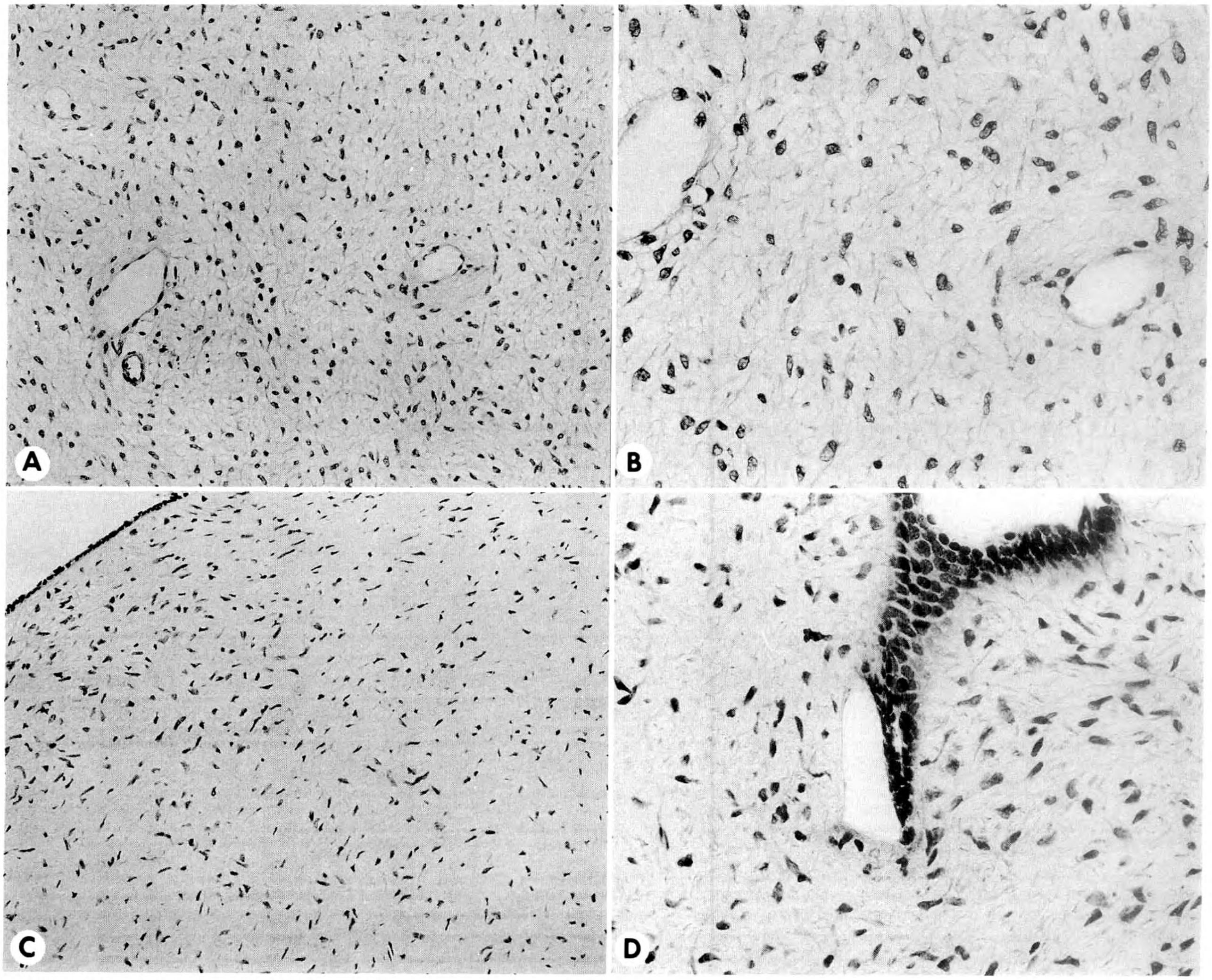

Fig 1. Dental follicles. A) With myxoid stroma and delicate vasculature (H & E, original ×80). B) Same follicle as in A (H & E, original ×200). C) With compressed epithelial lining on surface (H & E, original ×60). D) With palisading odontogenic cells (H & E, original ×200).

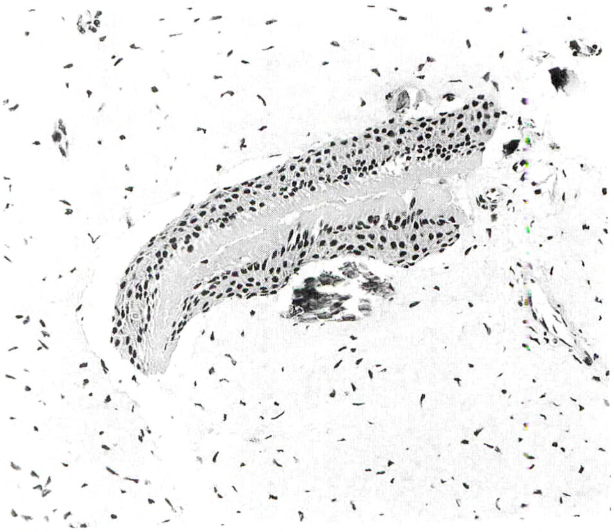

Fig 2. Dental papilla with more myxoid stroma than follicle and also showing focus of calcification next to detached odontogenic epithelium with dentin matrix (H & E, original ×80).

Radiologic and histologic findings serve to distinguish the follicles from neoplasms. Myxomas lack the epithelial lining found in many dental follicles.[3] The follicle is a well-demarcated, nondestructive, thin semicircular, and usually symmetric radiolucency around an unerupted tooth. Myxomas are larger than the usually no more than 3-mm-thick follicle and are more often poorly circumscribed, often expansile and destructive radiolucent lesions.

The greater myxomatous character of the dental papilla makes it more susceptible to misdiagnosis as myxoma than the dental follicle. Kim and Ellis[3] give helpful clues for identifying the papillae correctly. The papillae are easily separated from developing teeth during their removal or gross examination by the pathologist. The papilla is well circumscribed, elliptical, and less than 1.5 cm in diameter. The presence of odontoblasts, rimming the myxoid tissue, and an eosinophilic dentinoid tissue at the periphery (Fig 2) are further helpful differential diagnostic features.[3] Table 2 compares the salient features of the dental follicle and papilla with the odontogenic myxoma and fibroma.

ODONTOGENIC FIBROMA

The odontogenic fibroma has been subdivided into three types: hyperplastic dental follicle, simple, and WHO (World Health Organization) type.[4] Dentinoid and osteoid tissues in the WHO type readily identify that variant, but the simple type is often difficult to distinguish from a dental follicle and, at times, requires a combination of radiologic and histologic findings. Odontogenic fibromas are larger, less symmetric, and destructive, unlike the dental follicle.[3] An epithelial lining is not seen with odontogenic fibromas.[3]

TABLE 2. DENTAL FOLLICLE AND PAPILLA VERSUS ODONTOGENIC MYXOMA AND FIBROMA

Structure	*Salient Features*
Dental follicle	Lining epithelium (frequently fragmented and separated from connective tissue) Odontogenic epithelial rests (sparse) and calcification Stroma is variably myxoid fibrous connective tissue Closely applied to unerupted tooth Radiographically: well-demarcated, thin, usually symmetric radiolucency around unerupted teeth, nondestructive
Dental papilla	1.5 cm or less, well-circumscribed, elliptical Myxoid stroma May have rim of odontoblasts with eosinophilic dentinoid at periphery Nondestructive
Odontogenic myxoma	No epithelial lining Poorly vascularized myxoid stroma Poorly circumscribed, expansile, and destructive
Odontogenic fibroma	Simple type closely resembles dental follicle May have more islands of odontogenic epithelium than dental follicle No epithelial lining Destructive and larger than dental follicle

The odontogenic fibroma and the odontogenic myxoma show some morphologic similarities indicating a similar histogenesis (periodontal ligament and dental follicle). They are, however, separable, with the most distinguishing features between them being the abundance of collagen and the greater cellularity in the odontogenic fibroma.

INTRAOSSEOUS MYXOMA

Intraosseous myxoma is essentially a tumor of the jaws.[5-9] There is no exact counterpart in the rest of the skeleton.[9] Because of this restricted origin and the tumor's resemblance to the mesenchymal part of the tooth germ, an odontogenic origin is most likely, although derivation from nondental mesenchyme is also a possibility. The tumor is not common. Dahlin and Unni[9] indicate they had 35 cases of gnathic myxomas in their Mayo Clinic series of 8,542 bone tumors, an incidence of 0.41%.

Primary myxoma of the jaws is a histologically benign but locally aggressive tumor. Slow-growing and usually painless, it is nonetheless progressive and destructive, capable at times of producing severe

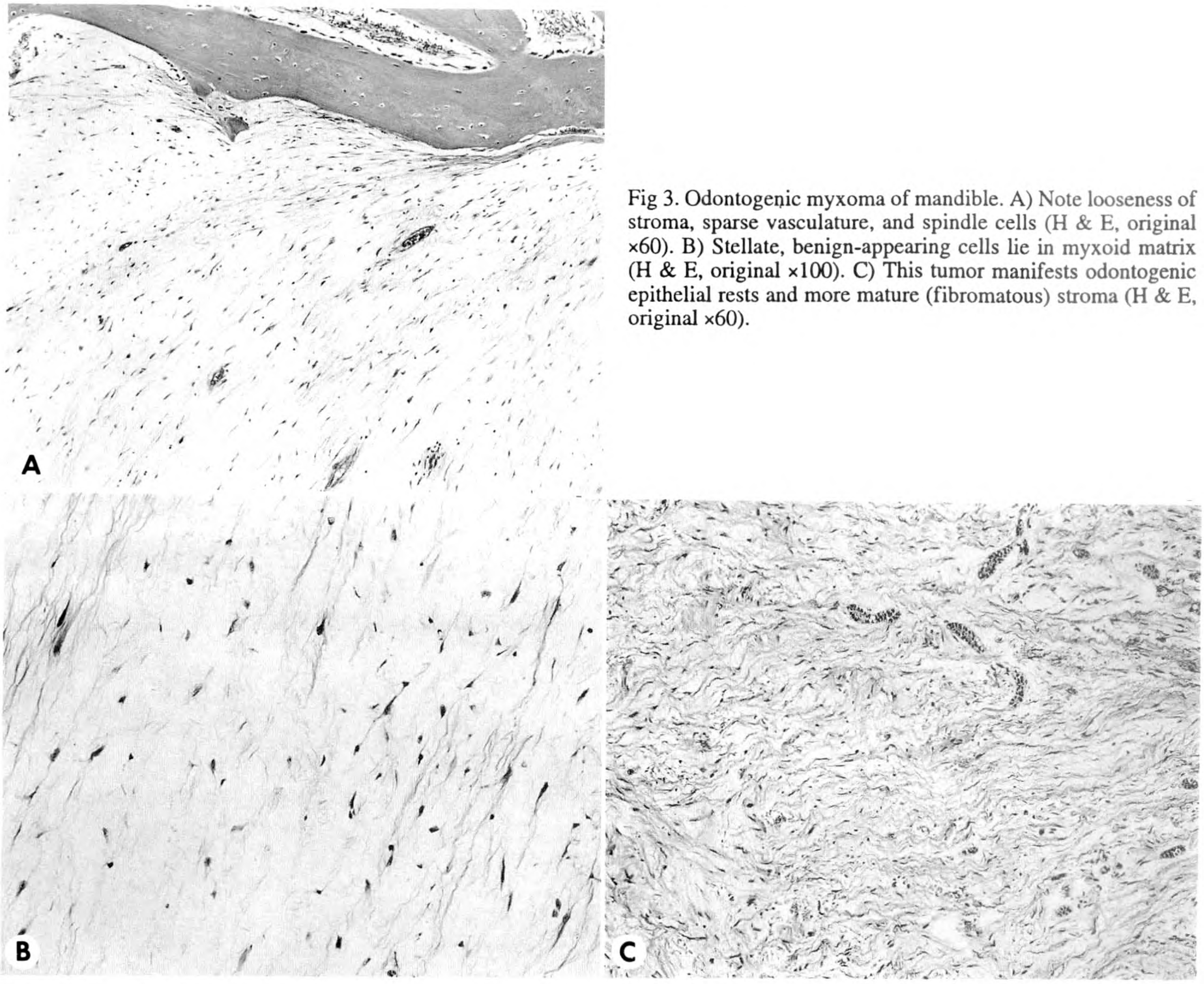

Fig 3. Odontogenic myxoma of mandible. A) Note looseness of stroma, sparse vasculature, and spindle cells (H & E, original ×60). B) Stellate, benign-appearing cells lie in myxoid matrix (H & E, original ×100). C) This tumor manifests odontogenic epithelial rests and more mature (fibromatous) stroma (H & E, original ×60).

facial deformity. There is no sex predilection for the tumor, which makes its clinical presentation in the second or third decades of life in 60% of cases. The age range is, however, wide and extends from 1.5 to 65 years.[5,9] There is a modest preference for the mandible, and the majority of the tumors are unilateral. With involvement of the upper jaw, the maxillary antrum may be filled by the tumor. Myxomas may be associated with absent or unerupted teeth, or the teeth may be displaced or mobile.[5] Occasional mandibular myxomas have occurred in non–tooth-bearing regions, but most myxomas of the mandible are found in the molar and premolar regions.[5]

Radiographs show an expansile radiolucency that is more often multilocular than unilocular. The latter have a less destructive behavior than the larger, multilocular tumors.[5] The lesions may be quite extensive and involve a condyle or an entire ramus or half a mandible or maxilla. Cortical expansion or thinning is followed by perforation.

On gross inspection, the myxoma is usually soft, often bosselated, and semitranslucent and manifests the slimy appearance of myxoid tissue. The typical histologic appearance is dominated by loosely dispersed stellate cells with long, interlacing cytoplasmic processes lying in an abundant, poorly vascularized, mucopolysaccharide-rich stroma (Fig 3A,B). Cellularity varies from hypocellular to a modest cellularity and a condensation of fibrous tissue (a fibromyxoma). Nuclei are typically uniform, and mitotic activity usually is not present. Strands of odontogenic epithelium may be seen, but are not necessary for the diagnosis (Fig 3C). There is a lack of correlation with cellularity and clinical behavior.[5,9] In the majority of the tumor cells, there is a high level of alkaline phosphatase and adenosine triphosphatase activity, similar to that noted in the odontoblasts of the dental pulp.[7,8] Three principal types of cells of the myxomas can be distinguished ultrastructurally: well-differentiated fibroblast, myxoblastic cell, and a cell type having morphologic features of the other two.[5]

Treatment of an odontogenic myxoma must consider its local destructive capacity and its potential for recurrence. Reports of surgical treatment include enucleation and curettage, peripheral resection with removal of the lesion with a 1- to 5-mm bone margin and maintenance of the inferior cortex, and wider resection with 1- to 1.5-cm margins.[8] Recurrence rates have approached 25%.[8] These may, in part, be due to the tumor's misleading apparent encapsulation. There is no capsule, and the infiltrative limits may be elusive, radiologically and intraoperatively. Odontogenic myxomas are not radiosensitive, and there has not been a study showing a long-term cure by radiotherapy alone.[8]

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CLINICOPATHOLOGICAL CONSULTATION

MORPHOLOGIC PATTERNS AND MOLECULAR PATHWAYS OF AIDS-RELATED HEAD AND NECK AND OTHER SYSTEMIC LYMPHOMAS

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Head and neck manifestations of human immunodeficiency virus (HIV) infection include lymph nodal and extranodal localization of non-Hodgkin's lymphoma (NHL). A histopathologic characteristic common to head and neck NHLs and to all the other systemic lymphomas in HIV patients is the frequent occurrence of cases displaying pleomorphic features and some overlap between established histologic subtypes. This article highlights the difficulties in defining HIV-related NHLs correctly, and proposes a specific pathologic categorization of these disorders accounting for their pathogenetic aspects as gathered from molecular data.

INTRODUCTION

Head and neck manifestations of human immunodeficiency virus (HIV) infection include enlarged neck nodes, nasopharyngeal lymphatic tissue hypertrophy, extranodal localization of lymphoma, Kaposi's sarcoma, multicystic benign lymphoepithelial lesions of the parotid gland, oral hairy leukoplakia, candidiasis, and other, less common illnesses, depending on the stage of the disease.[1-8]

Non-Hodgkin's lymphoma (NHL) is a relatively frequent manifestation of HIV infection, with extranodal involvement occurring in 68% to 85% of patients.[9-13] In patients with HIV infection, NHL may occur anywhere in the head and neck area. The tumor has been observed in a variety of sites, including the gingiva, palate, tongue, tonsil, nasopharynx, orbit, parotid, maxillary sinus, soft tissue, and hypopharynx.[14-21]

The morphologic features of HIV– or acquired immunodeficiency syndrome (AIDS)–related head and neck lymphomas are similar to those of other lymph nodal or extranodal systemic lymphomas occurring in the HIV setting. Most cases exhibit unfavorable histologic profiles, usually intermediate- or high-grade malignancy according to the Working Formulation (WF),[22] and express B-cell markers. Shapiro et al[18] reported on 19 AIDS patients in whom NHL developed in the head and neck region. Sixteen tumors were large cell (B-cell) lymphomas, and 3 were "small cell (B-cell) lymphomas." Nine instances of oral NHL occurring in HIV-infected homosexual male patients were evaluated by Green and Eversole.[15] Histologically, 2 cases were diagnosed as large cell lymphomas, 2 as "immunoblastic sarcomas," 2 as small noncleaved cell lymphomas manifesting Burkitt-like features, and 3 as NHLs not otherwise specified. In a recent study focusing on HIV-related head and neck lymphomas,[21] 17 of 28 cases could be categorized according to the WF,[22] and all of them were high-grade (14 cases) or intermediate-grade (3 cases) B-cell NHLs. The most frequent histologic types were small noncleaved cell (SNCC), Burkitt's type, and large cell immunoblastic. These data agree with previous reports of head and neck[15,18] and other AIDS-associated NHLs.[9-13] An interesting finding was the identification of a relatively high number of CD30-positive anaplastic large cell lymphomas (ALCLs) according to the updated Kiel classification.[23]

An intriguing pathologic characteristic common to head and neck NHLs and to all the other systemic lymphomas in HIV patients is the occurrence of cases having pleomorphic features, as well as some overlap between established histologic subtypes. This fact does highlight the difficulties in defining them correctly.

In an attempt to overcome some of these difficul-

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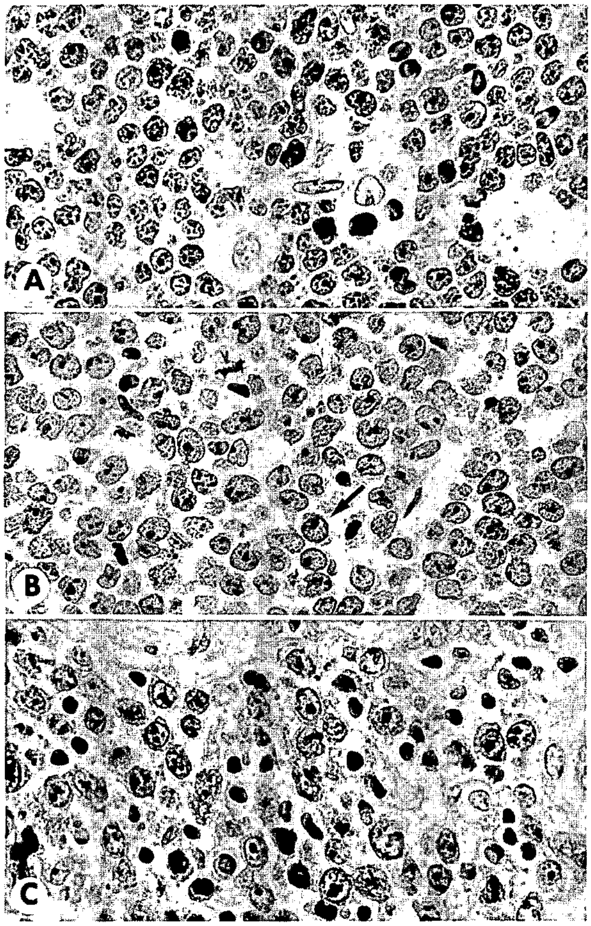

Fig 1. Acquired immunodeficiency syndrome–related lymphomas (H & E, original ×400). A) Small noncleaved cell, Burkitt's subtype. Monomorphic tumor cells are interspersed with macrophages. B) Small noncleaved cell, non-Burkitt's subtype. Tumor cells have irregular, sometimes eccentric nuclei (arrow). Larger cells with one or two larger nucleoli are also present. C) Non-Hodgkin's, with "intermediate" features. Medium-sized or larger tumor cells have large solitary nucleoli and are indistinguishable from immunoblasts.

ties, this paper focuses on challenging subtypes or variants, including those with morphologic features "intermediate" between established categories that have not been sufficiently considered so far. Furthermore, a list of morphologically determined subtypes is proposed in order to attain a more detailed and specific histopathologic categorization of HIV-associated lymphomas giving account of their pathogenetic aspects as gathered from the literature.

INSIGHTS IN PATHOLOGY

Classifying Lymphomas: Why So Difficult? In HIV-infected individuals most systemic lymphomas originate from B cells and fall within three WF[22] histologic categories: 1) large cell (G group), 2) large cell immunoblastic (H group), and 3) SNCC (J group). However, both SNCC and large cell (G and H groups) lymphomas in the HIV setting may exhibit pronounced polymorphism, with many large cell lymphomas showing various proportions of large lymphoid cells that display atypical, often multiple and bizarre nuclei. The most evident expression of this polymorphism can be found in CD30-positive ALCL.[9,24,25] Distinguishing between pleomorphic large cell lymphoma and CD30-positive ALCL is usually difficult, but tracing clear-cut morphologic borders between Hodgkin's disease (HD) and CD30-positive ALCL is even more difficult in the HIV setting.

Recently, it has been proposed to classify large cell and large cell immunoblastic lymphomas as a single category under the term diffuse large cell lymphoma (DLCL).[26] This category includes also B-cell CD30-positive ALCL.[26]

Low-grade B-cell lymphomas and multiple myeloma or solitary plasmacytoma are occasionally present in HIV patients.[9,27] T-cell lymphomas, including cutaneous T-cell lymphoma, lymphoblastic lymphoma, HTLV-1–associated T-cell leukemia, and peripheral T-cell lymphoma, have also been detected.[27] Not all these cases, however, are considered AIDS-defining conditions, and their incidence has not increased since the beginning of the AIDS epidemic.

SNCC Atypical Variant. In the general population the classic SNCC lymphoma category of the WF includes two main pathologic variants: the Burkitt's and non-Burkitt's subtypes (Fig 1). Both subtypes have been observed in HIV-positive European and American patients.[9,11] However, atypical SNCC, mainly made up of blastic cells exhibiting features "intermediate" between SNCC with plasmablastic differentiation and immunoblastic plasmacytoid cells, have also been described in HIV patients.[28,29] In this atypical variant—called the "immunoblast-like (large cell)" variant of SNCC by Lennert and Feller[30] —part of the tumor exhibits features of non-Burkitt's SNCC,[22] while the dominant histologic pattern is mainly composed of large cohesive cells and of reactive histiocytes in the background forming a starry sky pattern. The size of the tumor cells is very variable, small cells being also present. Several large cells exhibit a large single nucleolus and abundant basophilic cytoplasm as seen in immunoblastic plasmacytoid lymphomas[28] (Fig 1).

These atypical morphologic features sometimes prevent an accurate pathologic diagnosis of SNCC in HIV-positive individuals and may bias a correct discrimination of SNCC from immunoblastic lymphomas as required by their different clinical and biologic characteristics in the context of HIV infection.[11,13,27,28,31,32]

For these reasons a recent specific histopathologic

PATHOLOGIC CATEGORIZATION OF HIV-ASSOCIATED LYMPHOMAS AND THEIR MOLECULAR FEATURES

- "Blastic" cell lymphomas* (not associated with EBV-encoded LMP-1 expression)
  - Large cell (G-WF) (diffuse large cell lymphomas)
  - Small noncleaved cell (J-WF) (associated with *c-myc* deregulation plus p53 inactivation)
  - Blastic cell with intermediate features ("int")
- "Blastic" cell lymphomas (may be associated with EBV-encoded LMP-1 expression)
  - Immunoblastic (H-WF) (diffuse large cell lymphomas)
- "Anaplastic" cell lymphomas* (associated with monoclonal EBV infection and LMP-1 expression)
  - Anaplastic large cell (CD30/Ki-1+)
- Other (rare types and unclassifiable cases†)

HIV — human immunodeficiency virus, EBV — Epstein-Barr virus, WF — International Working Formulation for non-Hodgkin's lymphomas.

*Term "blastic" is used in analogy with suffix "-blastic" in Kiel Classification, while term "anaplastic" indicates undifferentiated cells displaying marked pleomorphism, with giant cells possessing bizarre and irregular nuclei and large nucleoli.

†Unclassifiable cases that do not fit into any definite category; unclassifiable cases because of poor histologic preparation or scarce amount of pathologic tissue.

categorization of HIV-related NHL has provided a provisional separate category for cases of difficult classification such as those presenting "intermediate" morphologic features[32,33] (see Table).

CD30-Positive ALCL. While the diversity in the molecular and immunophenotypic characteristics of AIDS-related SNCC and large cell, in particular immunoblastic, lymphomas has been assessed in recent reports,[34-37] few data are so far available on the characteristics of CD30-positive ALCL occurring in HIV individuals.[24,38-41]

CD30-positive ALCLs are a heterogeneous group of high-grade lymphomas at the borderline between HD and NHL. The presence of such lymphomas in the HIV setting was reported in some European series,[29,39,42] and they amounted to 4% of a large series of AIDS-related NHLs collected by the French Study Group of Pathology for HIV-Associated Tumors.[25] A recent report from the United States confirmed such occurrence also in North American HIV patients.[24]

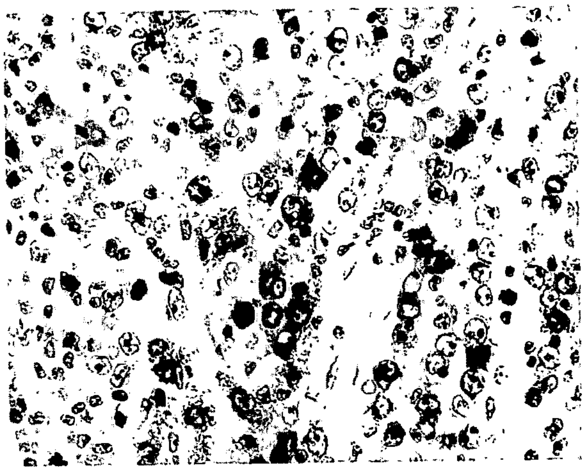

Fig 2. Acquired immunodeficiency syndrome–related CD30-positive anaplastic large cell lymphoma (alkaline phosphatase–anti–alkaline phosphatase method, hematoxylin counterstain, original ×250). Epstein-Barr virus–encoded LMP-1 cytoplasmic expression is seen on several tumor cells.

The morphologic features of CD30-positive ALCL include infiltration by large pleomorphic cells (often much larger than in usual large cell lymphomas) with abundant cytoplasm and irregularly shaped nuclei containing one or more prominent nucleoli, a high mitotic rate, presence of multinucleated cells often resembling Reed-Sternberg cells, fibrosis, and numerous macrophages intermingled with the tumor cells. Expression of CD30 antigen by all or almost all neoplastic cells is required for the diagnosis of CD30-positive ALCL; on the other hand, DLCL displaying features of the established high-grade NHL (pleomorphic immunoblastic or centroblastic; large noncleaved cell) should not be classified as CD30-positive ALCL, even if most tumor cells are CD30-positive. Furthermore, according to the International Lymphoma Study Group, large B-cell lymphomas that exhibit anaplastic morphology and typically express CD30 antigen (similarly to T-cell and "null" cell ALC lymphoma) should be diagnosed as morphologic variants of DLCL.[26]

MOLECULAR PATHWAYS AND MORPHOLOGIC PATTERNS

Human immunodeficiency virus– or AIDS-related lymphomas are characterized by distinct molecular pathways that selectively associate with specific morphologic types.

AIDS DLCL. A first major pathogenetic pathway is associated with AIDS DLCL. Because of the high frequency of Epstein-Barr virus (EBV) infection,[34,36] AIDS DLCLs have been thought of as EBV-driven lymphoproliferations. Since both EBNA-2 and LMP-1 are expressed by a fraction of EBV-positive AIDS DLCLs (immunoblastic subtype)[31,39] (see below), it is plausible that EBV is indeed a driving force for tumor growth and expansion. In this respect, AIDS DLCLs would be similar to lymphomas associated with congenital or iatrogenic immunosuppression, although AIDS DLCLs are consistently monoclonal.[34,36] In some cases, the monoclonality may be accounted for by the presence of genetic lesions of *c-MYC* and *BCL-6*.

AIDS SNCC. At the molecular level, AIDS SNCC is characterized by multiplicity of genetic lesions, including deregulation of c-*MYC*, inactivation of *p53*, and EBV infection in 100%, 60%, and 30% of cases, respectively.[34,36] Typically, EBV-infected AIDS SNCCs fail to express the viral transforming antigens EBNA-2 and LMP-1[31,39] (see Table).

AIDS ALCL. Whereas the molecular characteristics of AIDS SNCC and AIDS DLCL have been recently assessed, few data are available regarding AIDS ALCL pathogenesis. The large majority of AIDS ALCLs are associated with EBV infection of the tumor clone. In contrast with AIDS SNCC, EBV-infected AIDS ALCLs express the EBV-transforming latent genes EBNA-2 and LMP-1[29] (Fig 2). In a recent study reporting on the detection of EBV by in situ hybridization for viral DNA and RNA (EBER) carried out in 49 AIDS-related lymphomas, the large majority of CD30-positive ALCLs were associated with EBV (10/12; 83%), with a frequency of EBV detection similar to that of HIV-related HD and significantly higher than that observed in immunoblastic (3/7; 43%) or SNCC (6/15; 40%) lymphomas.[29] LMP-1 was restricted to ALCL, a proportion of immunoblastic lymphomas, and HD[29] (see Table). Concordantly, it has been demonstrated that HIV-associated immunoblastic lymphomas show heterogeneity regarding both the presence of EBV and latency pattern.[43]

How to Classify. In conclusion, the present paper shows the importance of an updated morphologic approach to AIDS-related head and neck and other systemic lymphomas through a specific classification taking into consideration the traditional subtypes and their molecular features (see Table). Our proposal takes into consideration 1) the need for a clear-cut diagnostic distinction between polymorphic "blastic" lymphomas and "anaplastic" ones, 2) the grouping of pathologic categories based on morphologic features and their probable association with different genetic lesions, and 3) the advantage of having a provisional category for cases of difficult classification such as those with "intermediate" morphologic features.

Such an approach to AIDS NHL may in turn provide a modern morphologic basis for further pathogenetically oriented investigations. To explore whether this proposal may be useful for the clinical management of patients with AIDS-related lymphomas, it should be tested in patients treated within large prospective studies. Some retrospective investigations trying to assess the value of the clinical application of the suggested pathologic categorization are in progress at our institute.[44]

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Otitis Media in Infants and Children

Second edition. Charles D. Bluestone and Jerome O. Klein. Hard cover, illustrated, indexed, 322 pages, 1995. WB Saunders, Philadelphia, Pa, $59.

This book is a collection of offerings on every aspect of otitis media by authorities who have pioneered and reviewed current information regarding its mechanisms and preferred treatment. There are 10 chapters that may be broken down into three general topics: 1) basic science of otitis media, 2) diagnosis and management, and 3) complications. To the clinician, the management section will prove to be most informative and prolific.

The authors convey the indications, straightforwardly, for tympanotomy tubes in the following cases: 1) chronic otitis media with effusion of 3 months' duration unresponsive to medical management; 2) recurrent acute otitis media to the extent of three episodes in the preceding 6 months if medical treatment has failed; 3) eustachian tube dysfunction as shown, eg, in posterior-superior quadrant or pars flaccida retraction, or both; 4) following tympanoplasty, if there are signs of loss of eustachian tube function; and 5) when a separate complication is present such as facial paralysis. These are premier indications.

Since each child with otitis media is unique, arbitrary reasons for tympanotomy tubes should include the patient's irritability, fussiness, and insomnia that result from the inflammatory state; and in those children who have preexisting conductive and sensorineural hearing loss in which performance and development in speech and language is suppressed because of this superimposed hearing loss from otitis media effusion, tympanotomy tube insertion should be much sooner, ie, 6 weeks rather than 3 months (reviewer's opinion).

The hallmark of this book is the review of the literature by the authors and their analysis of the data. There are scholarly management plans for each clinical condition in the various stages of infection and inflammation of the middle ear: acute otitis media, persistent middle ear effusion, otitis media with effusion, atelectasis and high negative middle ear pressure, and eustachian tube dysfunction. For instance, determining the causation for recurrent and/or continuing drainage following tympanotomy tube insertion is vigorously covered. A reason for the condition is reflux otitis media or contamination from the ear canal. Then a treatment option (after the usual treatment modes) is to remove the tube(s) — an ideal management for an annoying problem, but one not very often used in clinical practice.

There is not a detailed discussion of immunology in otitis media (all is not yet known), and the type of tube employed is not fully discussed (obviously, because of no recent studies on the subject).

This is a second edition. The bibliography is based on material reviewed since the 1988 edition.

It is admirable to have critical analyses and then convey visionary solutions like those Bluestone and Klein possess. This book is recommended to otolaryngologists and pediatricians, unless they possess Bluestone and Stool's *Pediatric Otolaryngology* (WB Saunders). Much of the information in this work appears in that textbook.

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Ménière's Disease. Perspectives in the '90s

R. Filipo and M. Barbara, editors. Hard cover, illustrated, indexed, 582 pages, 1994. Kugler Publications, New York, NY, $171.

This book is a collection of papers from the proceedings of The Third International Symposium on Ménière's Disease, Rome, Italy, 1993. One hundred ten papers comprise topics including chronic aspects, molecular biology and biochemistry, hydrops, pathology, electrocochleography, otacoustic emissions, vestibiology, endolymphatic sac, immunology, medical treatment, and surgery.

There remain two basic areas of controversy surrounding Meniere's disease, ie, the pathophysiology of the disorder and its treatment by both medical and surgical means. The very persuasive contention is that the vertigo of Meniere's disease is brought about by ruptures of the distended membranous labyrinth and consequently the perilymphatic spaces and nerve endings are perfused with solutions of potassium similar to endolymph. Increased endolymphatic pressure alone seems, at least clinically, not to cause vertigo.

Furthermore, it is surmised that the endolymph membranes are impervious to potassium (thus, a rupture of their membrane is necessary) but that potassium readily crosses the perilymphatic membranes and thus reaches the vestibular nerve endings. Potassium slows or blocks nerve conduction. The question then arises whether this nerve blockage of the diseased side is the cause of the vertigo, or whether it is the opposite, normal side that produces the sensation (personal communication, Fred Linthicum).

Treatment strategies for Meniere's disease are well covered. Several papers discuss medical treatment, which still is limited unless one considers gentamicin treatment a medical modality. Vestibular neurectomies have taken a preferred position over the shunt operation in this volume.

Main subject thrusts from these proceedings were research of Meniere's disease at the molecular level and electrocochleography, in which a point is made for testing with tone bursts, which have to be conveyed by transtympanic means (the amplitude of the waveform is larger, making it easier to interpret). There are no papers that compare extratympanic with intratympanic stimulations.

Only an author index is contained in this book. There is no subject index — a disadvantage to most proceedings books.

In summary, this book provides a number of important perspectives on our present knowledge of Meniere's disease, as well as pertinent and applicable material for the clinician.

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NEW YORK OTOLOGY AND NEURO-OTOLOGY UPDATE—1996

October 31, November 1 & 2, 1996

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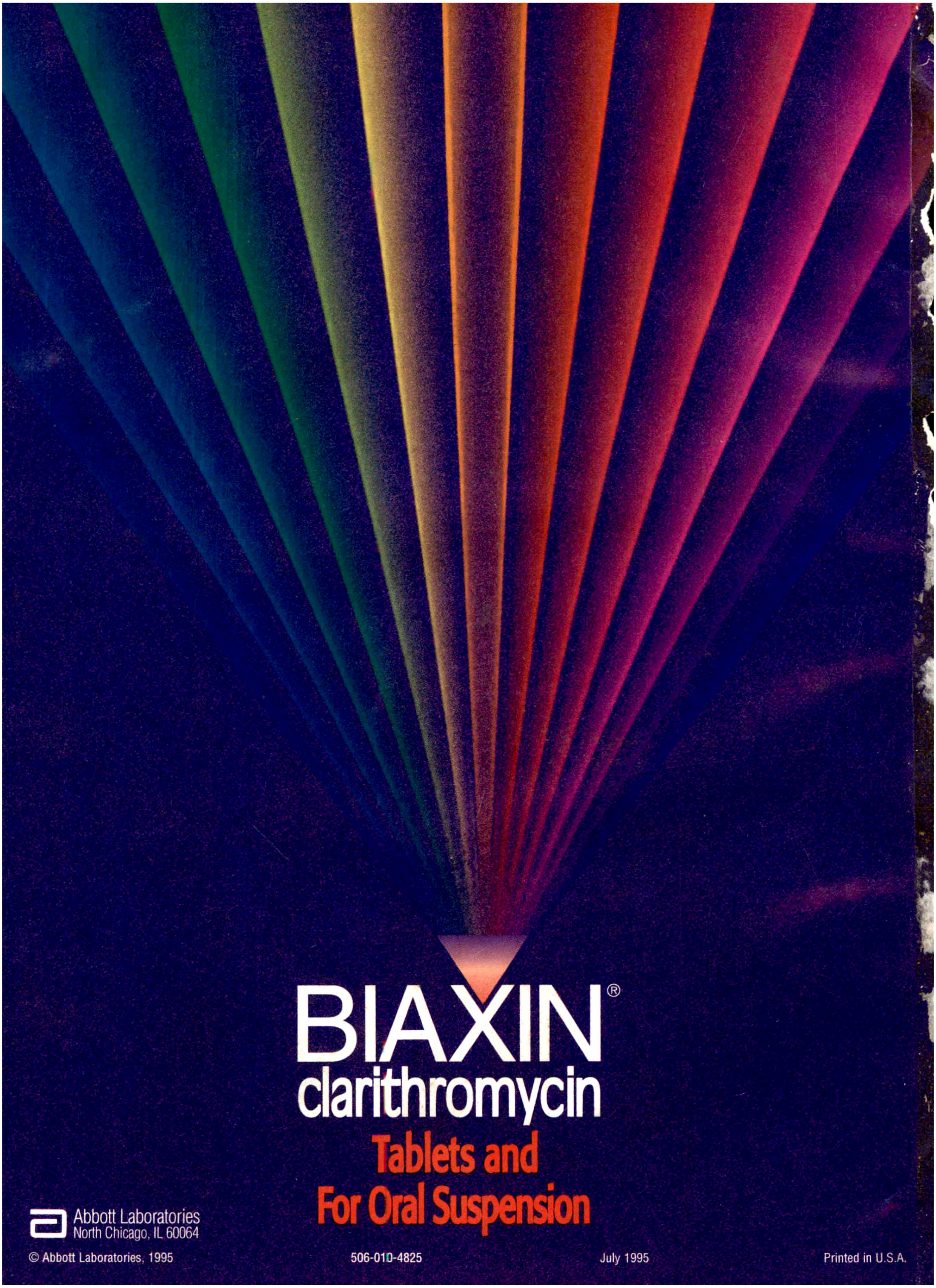

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